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MANAGEMENT OF POSTOPERATIVE PAIN

Rollin V. Oden, MD, *Guest Editor*

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Preface

Relieving pain is one of the most important tasks a physician accomplishes, yet it has been said that because treating pain is *everybody's* business, it becomes *nobody's* business; leaving patients without any member of the medical team responsible for relieving their pain. The usual postoperative pain prescription is intramuscular meperidine or morphine on an "as needed" schedule. There is little variation in the amount of analgesic prescribed or evaluation of the effectiveness of analgesic therapy. The patient will probably be given only a portion of the amount the physician prescribed and have a recurrent cycle of pain, sedation, pain relief, pain. The patient may have adequate blood levels of analgesic medication for as little as a third of each dosage interval. This scenario occurs because very little medical education is devoted to teaching physicians how to effectively treat pain. Unfortunately, because of barriers in knowledge, skills, and attitudes of health care professionals and barriers in the health care system, state-of-the-art analgesic care is not available to all, or possibly even very many, of the 20 million patients who suffer acute postoperative or trauma pain in the United States each year. The efficacious treatment of acute postoperative and post-traumatic pain is a serious deficiency in modern health care. Effective means of controlling acute pain are available. In this issue the extent of the problem of acute pain treatment is explored; the neurophysiologic-pharmacologic basis of nociception is explained; the psychological concomitants of acute pain portrayed; and effective techniques of acute pain control delineated.

A number of discoveries and innovations have led to advances in neuropharmacology and analgesic techniques. These include the discovery of endogenous opioids and the spinal modulatory pathways. The discovery that spinally administered opiates produce analgesia in animals and man has revolutionized the ability of physicians to insure effective analgesia for a large number of patients. The development of infuser technology for patient-controlled analgesia has now reached the second generation of machines that provide both continuous and patient demand modes. But there is more to relieving acute pain than just the use of potent opiate analgesics. The psychological state that the patient brings to the hospital needs to be recognized and assessed; the psychological effects of acute pain need to be understood and nonpharmacologic interventions employed when efficacious. There are a number of nonopiate and adjuvant medications, such as the nonsteroidal anti-inflammatory drugs, anticonvulsants, and antidepressants, which are routinely used in chronic pain management, but are under-utilized in the treatment of acute pain. There are new analgesic techniques such as intrapleural local anesthetic instillation and combined epidural local anesthetic and opiate infusions that are effective for certain patients. These techniques, if systematically applied, will be effective in relieving the suffering of patients with acute pain. It is the humanitarian goal of all physicians to relieve their patient's pain, but their patient's well-being may also be improved if their pain is better controlled.

It is not enough to simply recognize that under-treatment of acute pain occurs and to trust that with continued innovation and pharmaceutical research the day will come when "no patient should . . . have to suffer needless pain because of incorrect assumptions or lack of information among health professionals." A proactive approach is needed to address the barriers to effective pain control in each hospital. This proactive approach needs to cut across the lines of medical territoriality to place health professionals with the most ability, regardless of specialty, in charge of controlling the patient's pain. Teams are needed that are composed of nurses, physicians, psychologists, social workers, and clergy to effectively address the multifactorial nature of pain. The health care system needs to be held accountable by the accrediting agencies for effective pain management. The curricula of our nursing, pharmacy, and medical schools need to teach effective pain assessment and treatment techniques. And finally, patients need to be taught that unrelieved pain is not the sentence that modern surgery must impose; that they can expect and have the right to have their pain relieved and their suffering assuaged. In the words of Judith Spross, "Pain *is* an emergency for the person who experiences it regardless of the urgency of the underlying pathology. I believe we must apply the science and art of pain relief as though a life depended upon it. Certainly the quality of life does."

The contributing authors for this issue have admirably written succinct reviews of the state-of-the-art techniques of analgesia and analgesic pharmacology, which I think the practicing clinician will find instructive and stimulating. In a recent editorial in *Anesthesiology*, Saidman exhorted anesthesiologists to take the leadership in improving acute pain treatment: "An entirely new and nearly open-ended opportunity awaits our specialty, and we should grasp the chance while it is before us." I would hope that this volume will serve as a guidebook for anesthesiologists to take this leadership role and become the *somebody* responsible for relieving acute pain.

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Acute Postoperative Pain: Incidence, Severity, and the Etiology of Inadequate Treatment

*Rollin V. Oden, MD**

Pain—has an Element of Blank—
It cannot recollect
When it begun—or if there were
A time when it was not—

It has no Future—but itself—
Its Infinite contain—
Its Past—enlightened to perceive
New Periods—of Pain

EMILY DICKINSON

In the United States each year, 21.5 million surgical procedures are performed.[2] Many patients will suffer uncontrolled pain. This is an indictment of modern health care that has repeatedly been decried in editorials and journal papers for 25 years.[19, 34, 36, 39] The treatment of postoperative pain has been described as "the grave defect in English public hospital treatment which . . . is a cruel and callous disgrace."[26] An obstetrician stated that his pain after open heart surgery "defied description."[9] Despite this attention, the incidence and severity of postoperative and other acute pain states remains poorly understood by members of the health care community. Lord Kelvin stated, "If a thing exists, it exists in some amount." Pain exists and it exists in some considerable amount.

A great deal of effort has been devoted to determining how to best measure pain, but first it is necessary to define what it is that one is trying to measure. The International Association for the Study of Pain (IASP) has endorsed the definition put forth by Merskey: Pain is the sensory and emotional experience associated with actual or potential

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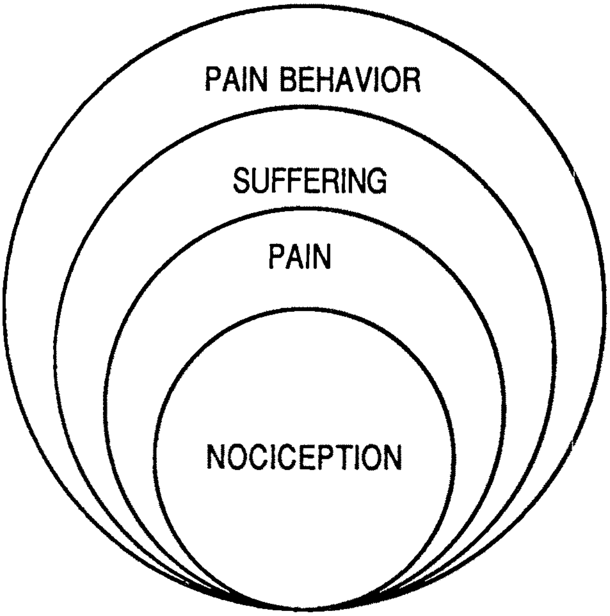

Figure 1. A multifaceted model for the components of pain. (*From* Loeser JD: Concepts of pain. *In* Stanton-Hicks M, Boas R (eds): Chronic Low Back Pain. New York, Raven, 1982, p 146; with permission.)

tissue damage or described in terms of such damage.[31] One cannot determine for the individual patient how much nociception occurs in response to tissue damage, nor infer from the surgery performed, body surface area burned, or the number and types of bones broken how much pain the patient "should" have. One has to rely on the expressions of the patient to accurately measure the subjective nature of pain. A useful model is the multifaceted one developed by Loeser of the Multidisciplinary Pain Center at the University of Washington and illustrated in Figure 1.[25] At the core of this model is the unmeasurable nociception resulting from tissue damage. The next layer, also not available to direct inspection, is the human experience comprising emotional and sensory components integrated to form "pain." Pain leads to suffering and suffering to pain behaviors. Only the pain behaviors are available for observation. Pain behaviors can span the range from withdrawing to grimacing to crying out to asking for analgesic medication. The subjective nature of the pain experience does not, however, preclude its measurement because pain is simply "what the patient says hurts." Thus, if one relies on the patient's report of pain, it is possible to measure pain intensity and the response to analgesic intervention.

PAIN MEASUREMENT

There are a wide range of measurement techniques that have been used for the measurement of both clinical and experimental pain in human beings. Pain measurement is too large a topic to be reviewed here but the interested reader is referred to the excellent work by Melzack.[29] Accurate pain measurement relying on the patient's self report can be as simple as the classification of pain into simple descriptors of intensity ranging from "none" to "excruciating," or the intensity can be measured numerically using ratings from 0 to 100. The most popular simple method is the visual analog scale (VAS) described by Aitken for the measurement of subjective states.[1] The patient makes a slash mark depicting his pain intensity on an unmarked line of fixed length (usually 100 mm) anchored at one end with "no pain at all" and the other end with "worst pain possible or imaginable." The mark is measured from the left-hand end and reported in mm from 0 to 100. This technique is understood by most patients (about 90 per cent) and is useful for both clinical and research purposes. An intuitively simple and clinically relevant rating scheme was used by Austin et al in their study of meperidine pharmacokinetics and dynamics.[3] The patients were queried as to the absence or presence of pain, ranked 0 or 1, and whether the patient desired more analgesic medication, ranked 2. This scheme is very simple and yet addresses the essence of the problem for the patient: is pain present and if it is, does the patient desire more pain relief with additional analgesic medication? Other methods for the measurement of pain rely on questionnaires, such as the McGill Pain Questionnaire (MPQ), which attempts to separate the sensory and affective components of the pain experience.[29] Useful methods for measuring the effects of analgesic interventions have been developed and include the total pain and analgesia relief (TOTPAR) and sum of pain intensity differences (SPID) methods.[15] Although there is no absolute consensus on how clinical pain should be measured, there is enough agreement that clinicians and researchers do not have to despair of being able to measure the subjective phenomenon of pain. A number of studies of acute pain have been completed. Studies of the incidence and severity of postoperative pain can be divided into three groups historically and by the nature of the study.

POSTOPERATIVE PAIN STUDIES

The first group are the studies that assess the incidence and severity of pain by measuring the amount of analgesic medications that patients use in the postoperative period. This method is "proxy" pain assessment because pain itself is not measured but inferred from a second measure, the amount of analgesics consumed. The second group of studies are those that measure the incidence and severity of pain in selected populations to establish accurate descriptions of the postoperative pain experience after various surgical procedures and in other medical situations accompanied by acute pain. These studies have employed a variety of pain assessment techniques including both ad hoc and more rigourously standardized questionnaires. From these studies an appreciation is gained of the significance of the postoperative pain problem. The third group of studies are those that are "interventional" in nature. These studies compare various treatment techniques for postoperative pain and can inform us as to the nature of the pain experience in conventionally treated patients who serve as the control group. Although many studies cannot be easily categorized into one group and bridge groups, this classification system is useful to place the studies in perspective. In a recent review it was stated that the exact "incidence, intensity, and duration of pain experienced by patients after various operations are not precisely known."[5] Although in large part this remains true today, from these groups of studies a picture emerges of the extent of the problem of inadequate acute pain treatment, which is worth reviewing.

One of the earliest studies of postoperative pain is the study by Parkhouse et al in 1961.[33] Approximately 1000 patients were studied by having the postoperative care nursing staff record the number of injections of analgesics that the patients required for 48 hours following their operation. The single factor studied that correlated with the amount of analgesic medication that patients received was the anatomic site of operation. The ranking by site from most injections to least was upper abdominal gastric surgery > gall bladder > lower abdominal > appendectomy > inguinal herniorraphy. Very few patients in any group required no injections at all and when analyzed by age, patients over 50 years of age required fewer injections than patients under 50 years. From this study the authors concluded that the "... routine prescribing of drugs will not do ... in any group of patients there is wide variation in the therapeutic need." Benedetti, Bonica, and Bellucci in their review of postoperative pain summarized the data from a number of studies to come to similar conclusions that pain is more severe after thoracic, abdominal, spine, and major joint surgeries. In contrast, superficial operations of the skin, head, and neck are associated with a lower incidence and severity of pain.[5] The authors further concluded that pain is highly variable between patients, hospitals, and even countries.

Patient age effect on postoperative pain has been addressed by Bellville et al.[4] The SPID scores of 712 patients who were enrolled in the Veteran's Administration Cooperative Analgesic Study were tabulated. Ninety four per cent of the patients had postoperative pain and were given intramuscular morphine and/or pentazocine. Linear regression analysis of SPID versus age showed slopes of 0.039 and 0.052, respectively, for the two drugs. There was poor correlation between pain relief and height, weight, and body surface area. When the data were further analyzed to account for both age and site of operation, age continued to be the best predictor of pain relief in response to analgesics administered. Kaiko et al[21] examined the effect of age on pain relief and found that the elderly responded as though they had received 3 to 4 times the amount of morphine as compared with younger patients. However, the *duration* of analgesia rather than peak analgesia intensity was increased, suggesting that the analgesic was cleared more slowly from the body. This was corroborated by the pharmacokinetic data. From these studies it should not be concluded that the elderly have decreased pain, but that they have an increased response to analgesics explained by changes in the pharmacokinetics of analgesics that occurs with advancing age.

The second group of studies that warrant review are the descriptive studies of patients and their pain reports. The most frequently quoted study on the undertreatment of patients suffering acute pain is that by Marks and Sachar from 1973.[27] They studied 37 hospitalized medical patients by patient interview and chart review. They found that 32 per cent of the patients reported severe distress from pain, 41 per cent were in moderate distress from pain, and 29 per cent reported marked impairment in ability to sleep from unrelieved pain. The most significant aspect of this study, however, was the discrepancy found between the amount of analgesic medication prescribed and that actually received by the patients. The average amount of intramuscular meperidine prescribed was 360 mg per day, but the amount the patients actually received averaged only 90 mg. Patients were actually given only one quarter of the amount of medication prescribed! Further analysis of the amount of medication received, according to severity of distress of pain from severe to minimal, showed little differences between the groups in the amount of medication received. This study was conducted in medical patients and its applicability to postoperative pain has been questioned. Donovan et al[11] conducted a similar study in 1987 in 353 hospitalized medical and surgical patients. The patients were equally distributed between medical and surgical services and the participants completed a questionnaire composed of portions of the MPQ. Analgesic medication use was tabulated from chart review. Forty-three per cent of the patients admitted to being in pain at the time of the interview. Sixty-one per cent of the patients reported being awakened from sleep by pain, and 203 patients reported experiencing "horrible or excruciating" pain at some time during their hospitalization (only 21 of these episodes were associated with a painful procedure). Medication use was converted to morphine equivalents using standard conversion ratios. The average amount of morphine or its equivalent prescribed was 50.9 mg per 24 hours. The average amount the patients actually received was 12.4 mg. Alarmingly, 15 years after the Marks and Sachar study, hospitalized patients still may receive only one quarter of the amount of analgesic medications prescribed and still report significant unrelieved pain.

The effectiveness of analgesic medications for postoperative pain was surveyed by Melzack et al utilizing the MPQ.[30] Eighty-eight patients who were receiving medications for postoperative pain were studied at the time of receiving their routinely ordered analgesic medication. Studies were carried out from 1 to 18 days after operation and the MPQ was administered before and after analgesic therapy. The authors determined that there appear to be two distinct groups of patients: those who recover as expected after surgery and whose pain resolves in a relatively short period of time (under 4 days), and a second group whose pain persists beyond the fourth postoperative day. In the latter group their pain was less well controlled with analgesics; some patients reported an increase in pain after analgesic therapy; they were prescribed lower doses of medication and received them more frequently; and they tended to be older patients with more medical problems.

This second group of studies has demonstrated that many patients when queried directly regarding their postoperative pain experience report unrelieved pain despite analgesic therapy and that often the patients are only receiving a portion of the amount of analgesic medication prescribed. It should come as no surprise that if physicians underprescribe and the prescription is further reduced by nurses, that patients are left with considerable unrelieved pain.

The third group of studies that are important to review are those studies comparing various analgesic interventions. These studies are of value because the control group receiving conventional analgesic therapy informs us as to the nature of pain experienced by the "usual" patient on the postsurgical ward. Two recent innovations in postoperative analgesic care that have yielded a large number of studies for review are spinal (epidural and intrathecal) opiate analgesia and patient-controlled analgesia (PCA). There are far too many reports to review comprehensively here, but more complete discussions are found in the articles that follow. Two studies that are exemplary are the studies by Eisenach et al[13] and Harrison et al[18] comparing intramuscular morphine or meperidine, epidural morphine, and intravenous morphine administered by PCA for patients having postcesarean delivery pain. In both studies patients were randomly assigned to each group and pain assessments were made for 24 hours postoperatively. In the work by Harrison, 94 per cent of the patients given intramuscular analgesics reported moderate to severe pain throughout the observation period. In Eisenach's study there were significantly more observation periods (approximately 27 per cent) in the intramuscular analgesic group when patients reported being very uncomfortable or in pain. These studies demonstrate that conventional analgesic therapy of intramuscular opiates prescribed on an as needed basis is poorly effective at controlling a large number of patients' postoperative pain.

Why is it that "conventional" intramuscular as necessary dosing of analgesics are ineffective? The foregoing studies demonstrate that patients do not receive all of the medication prescribed in many cases, but the problem is not simply that. Austin et al examined the pharmacokinetics and dynamics of fixed dosing (4 hourly) meperidine in a group of postsurgical patients.[3] They concluded that in the first 24 hours postoperatively patients' serum meperidine levels exceeded analgesic threshold concentrations only 35 per cent of the time. This was reflected in the pain scores obtained. In a study of pharmacokinetics of gluteal muscle administration of morphine, the time to peak plasma concentrations varied from 4 to 60 minutes.[35] There are also very large differences in the plasma levels attained between deltoid and gluteal administration.[16] The use of "as needed" prescriptions sentences the patient to recurring cycles of pain and either inadequate pain relief or sedation depending on the dose given. It may be concluded that while traditional intramuscular as necessary dosing of analgesics is simple and inexpensive, it falls short of the mark in effectively achieving control of acute pain. This regimen is persistently used because of tradition, lack of knowledge and skills, and attitudes of the physicians responsible for prescribing analgesic medications.

PHYSICIAN KNOWLEDGE AND ATTITUDES

The knowledge and attitudes of medical staff about pain relief have been examined in a number of studies. In the previously mentioned study by Marks and Sachar, the researchers also administered a questionnaire to medical residents about treatment alternatives in analgesic therapy.[27] One hundred per cent of the respondents stated they aimed for complete pain relief or pain relief that provided freedom from distressing pain. It must be remembered that in the same institution the average analgesic dose prescribed was meperidine 360 mg per 24 hours and that 32 per cent of the patients reported severe distress from pain. This is not an indictment of the individuals or the institution, but demonstrates that despite motivation to relieve pain, deficiencies in knowledge and skills preclude effective pain relief. They also found that the physicians surveyed underestimated the effective dose of meperidine and overestimated its duration of action. Sixty per cent of the respondents correctly answered that the risk of addiction to opiates, when used for acute pain treatment in a medical setting, was less than 1 per cent. These results contrast to the findings of Weis et al in a similar study of housestaff and nurses who found that only 23 per cent and 21 per cent, respectively, had complete pain relief as the goal of therapy and only 16 per cent and 11 per cent correctly estimated the risk of addiction.[41] Grossman and Sheidler studied the skills of medical students and house officers in prescribing narcotic medications using three patient management vignettes.[17] This study demonstrated that the students and physicians in training had few skills for determining equivalent doses of medications, but after instruction in how to use narcotic equivalency tables improved their ability to determine how to change patients from one opiate to the equivalent dose of another. A review by the author of five major textbooks of surgery encompassing greater than 10,000 pages of text found only seven pages devoted to postoperative pain treatment and three of the books made no mention whatsoever.

NURSE KNOWLEDGE AND ATTITUDES

It has been demonstrated that physicians underprescribe opiate analgesics and that patients receive much less than prescribed. Nurses are most often the caregiver actually choosing the type and dose of analgesic medication administered, so it is appropriate to examine the factors that influence nurses' medication choices. Cohen studied why nurses choose the doses of medications they administer.[7] Nurses were surveyed using clinical vignettes regarding their medication choices. One third of the nurses would give a medication ordered every 3 to 4 hours as needed only when requested by the patient. In a second vignette the nurses were asked to choose the dose of meperidine to administer to a robust 250-lb male postoperatively for whom the physician has ordered 50 to 150 mg every 3 to 4 hours as needed. Only 7 of 121 respondents would give more than 100 mg. When told that this patient had received 50 mg 3 hours previously, was complaining of severe pain, and that pain relief was minimal from the previous injection, again only seven nurses chose a dose higher than 100 mg. Yet when asked an objective question about the effective dose of meperidine for such a patient, 46 nurses correctly chose an adequate dose. The same nurses were asked to list the criteria by which they made medication choices. Only about a third used the severity of pain and only a quarter the patient's response to the previous medication as criteria for determining the next medication choice. As a second part of the study the author surveyed 109 surgical patients using a structured interview similar to that of Marks and Sachar. There are several very interesting results of this survey. Nearly 80 per cent of the patients stated that pain relief was adequate, but 67 per cent reported pain disturbed their sleep, and half of these reported marked disturbance. Seventy-five per cent of the patients reported marked distress from pain. When the patients' charts were reviewed it was found that 90 per cent of the patients with severe pain were receiving less medication than ordered. From this study there appears to be a discrepancy between nurses' knowledge and practice.

Morgan and coworkers reviewed the charts of 106 patients having cholecystectomy.[32] The average amount of analgesic medication prescribed when converted to meperidine equivalents was 634 mg per 24 hours (± 162 mg). The amount the patients actually received over the first 3 days postoperatively was 486 mg, which was 29 per cent of that ordered. The researchers further analyzed their data to determine if there were other factors that correlated with the amount of medication the patients were prescribed and received. There was no correlation with age, but there was a significant correlation with the weight of the patient: increased amounts of medication were prescribed but there was no increase in the amount received. Less medication was given to patients who did not have private insurance and less was given to patients who were nonwhite. These are very disturbing findings that need to be corroborated. If found to be true, significant revisions in patient care attitudes are needed.

In another study assessing the effects of caregiver knowledge and attitudes on acute pain therapy by Chapman et al, nurses in a Brisbane hospital were studied.[6] Seventy-four per cent thought that most patients received adequate pain relief, and 68 per cent thought an intramuscular analgesic was effective for 4 hours. Less than half thought patients should be given intramuscular analgesics for as long as needed, and 36 per cent thought only for 48 hours postoperatively. Encouragingly, 76 per cent stated they offered pain medications more often than the patient requested them; 92 per cent recognized the variability between patients in analgesic requirements; and 87 per cent thought intravenous analgesics would be more beneficial than intramuscular injections of the same drug. However, 27 per cent were concerned that acute pain therapy with opiates may lead to addiction (one has to wonder about the effects of social desirability on the results recorded in this type of survey study). When asked which physician they felt was most appropriate to prescribe postoperative analgesics, 40 per cent chose the anesthetist and only 19 per cent the surgeon. Watt-Watson found that no student nurses felt hospital patients should tolerate severe pain, but 5 per cent of graduate nurses did.[40] Yet 60 per cent of the student nurses felt that patients should be encouraged to tolerate more pain and unfortunately 49 per cent of the graduate nurses responded similarly. Two thirds of the nurses in both groups thought that the risk of addiction in hospital patients treated with opiates was greater than 10 per cent and 73 per cent thought the rationale for as needed dosing was to prevent addiction. When asked about the usefulness of placebos to determine if pain was "real," 62 per cent responded affirmatively. When asked about the duration of commonly used analgesics, over 50 per cent incorrectly overestimated the duration of action for morphine, and 75 per cent overestimated meperidine's duration of effect.

Dudley and Holm further examined characteristics of nurses that may affect pain management choices.[12] They found that nurses tended to infer greater psychological distress than pain. The implication from this research is that the patient with serious illness is not experiencing pain, but suffering from psychological distress. This may have serious implications for how nurses choose analgesic therapy. The patients may be given psychological support but not the analgesic they need to obtain pain relief. Lenburg et al further examined inferences of pain and psychological distress in four different occupational groups: nuns, teachers, physicians, and nurses.[23] Two of these, the latter groups, were involved in patient care. All groups inferred greater psychological distress than physical pain. Nuns inferred the highest amount of physical pain of the groups studied and physicians the least. The authors postulated that nurses and physicians may develop adaptive responses to insulate themselves from the constant emotional stress of observing the pain and illness of others. Iafrati[20] examined the differences between patient and nurse perceptions of burn patients' pain. Patients and nurses were studied using visual analog scales immediately after wound cleansing and dressing changes, an intense nociceptive experience. The patients and nurses rated how much pain the patient had during the procedure. The nurses underestimated, overestimated, and correctly estimated the patient's pain almost equally. When over- and underestimates were stratified by nurse characteristics, new graduates, new burn unit nurses, degree program trained nurses, and nurses over 30 years of age were found to *overestimate* pain, while veteran burn unit nurses, diploma graduates, and nurses under 25 years of age *underestimated* the patient's pain.

Ketovuori[22] examined nurses ability to accurately estimate patient's wound pain perceptions after laparotomy. The nurses were stratified by whether they themselves had ever had surgery. Interestingly, nurses who had not had previous surgery tended to overestimate wound pain while non-naive nurses' estimates more closely approximated the patients' ratings. As in the previous studies, a very low percentage (8 per cent) of the nurses responded that the goal of analgesic therapy was to relieve pain completely. Only 37 per cent correctly responded that the risk of narcotic addiction was 1 per cent or less. Teske et al[38] examined inter-rater reliability between trained nurse observers assessing pain and reliability between patients' perceptions of pain and the nurse rater's estimate of pain. The nurse estimations of the patient's pain were made on the basis of observation of behaviors that are often thought to be indicative of pain such as frowning, grimacing, and tenseness. In addition, a VAS for pain was used by the nurse and patient. While the nurse inter-rater reliability was very high (Pearson correlation 0.78) the correlation for nurse and patient were much lower (0.41). From these studies it is clear that pain is a subjective phenomenon that is best judged by the patient rather than inferred by the observer.

The inadequacy of acute pain relief cannot all be laid at the feet of the physicians and nurses, however. The patients and their families are also an important determinant of the adequacy of pain control. There appears to be a discrepancy between the patients' reports of pain and their satisfaction with analgesic therapy.

PATIENT ATTITUDES AND THE HEALTH CARE SYSTEM

Donovan examined general surgical patients in a study of patient attitudes toward postoperative pain relief.[10] Eighty-six per cent of the patients reported satisfaction with their postoperative pain relief despite the fact that 62 per cent reported significant pain. When queried as to why they were satisfied with pain relief despite unrelieved pain, 75 per cent of the patients responded that it was because they expected pain after their operation; 52 per cent because the pain was less than expected; 50 per cent because they knew they would get better; and 26 per cent because they knew why they had pain. As in other aspects of life, it would appear that the relationship between expectation and actualization is an important determinant of satisfaction. It is to be hoped that patients will become more aware that their pain can be relieved and that they do not have to expect unrelieved pain as a necessary sequelae of surgery.

The psychological factors that influence patient's perceptions and reports of acute pain are discussed more fully in following articles, but patient factors that affect analgesic medication use are worth considering briefly. Taenzer studied patients undergoing elective gallbladder surgery using the MPQ, VAS for pain and distress, the State-Trait Anxiety Inventory, and the Beck Depression Inventory.[37] This study showed that although there was a weak but significant correlation ($r = 0.26$) between pain measures and the total amount of narcotics administered, there was a stronger correlation ($r = 0.44$) between situational anxiety and analgesic requirement. Patients may receive narcotic analgesics for anxiety that would be better treated with anxiolytics or nonpharmacologic interventions. Anxiety in the surgical patient is more fully discussed in the article by Egan in this issue.

Pain is a dehumanizing experience that destroys the soul. Lisson, writing on the ethics of pain control quotes from the Book of Sirach: "One hour of pain destroys all pleasures."[24] Why then is pain allowed to go unrelieved? Lisson postulates that patients are reluctant to complain because of concerns of burdening the nurses, fear of addiction, and because of the verbal and nonverbal messages they receive from health care professionals that increase the patient's feeling of dependency. Medical sociologist Mauksch notes that the goal of the hospitalized patient is to survive the hospital experience.[28] When entering the hospital each patient receives a limited number of "care chips" that they must play with the skill of the veteran gambler. To squander their "care chips" threatens their ability to survive hospitalization. The sociologist's view are further expressed by Fagerhaugh and Strauss who trace the pain relief problem to the fact that no one member of the medical team is actually responsible for relieving pain and that the task orientation of the health care team ignores how the patient actually feels.[14] In addition, interactive "political" processes are used by the health care team to persuade, threaten, cajol, and bargain the patient into conforming to the organizational needs of the health care system.

BARRIERS TO ADEQUATE ACUTE PAIN CONTROL

From the foregoing studies a picture has emerged that all is not well on the postsurgical units of our hospitals. A large proportion of patients suffer unrelieved pain that interferes with their ability to sleep and ambulate; and in many cases their pain is "excruciating or horrible." The first question that must be answered is are there methods available that can be used to effectively and safely treat postoperative pain? There is compelling evidence from the third group of studies reviewed that there are readily available means of safely con-

Table 1. *Barriers to Effective Pain Control*

Knowledge and skills

1. Lack of understanding of the pathophysiology, neural pathways, and neuropharmacology of acute pain
2. Lack of knowledge of pharmacology of commonly used analgesic medications
3. Lack of knowledge of usefulness and underestimation of the effectiveness of nonnarcotic analgesics, co-analgesics, and adjuvant medications
4. Lack of knowledge of new analgesic medications and new methods of pain relief
5. Lack of skills in assessing pain
6. Lack of knowledge about the variety of analgesic medications available, which can be confusing
7. Overestimation of the risks associated with potent analgesics
8. Lack of knowledge of the differences between tolerance, physical dependence, and addiction
9. Lack of skills in regional anesthetic/analgesic techniques
10. Lack of knowledge about the effects of fear and anxiety on pain and pain relief
11. Lack of knowledge about the effects of preoperative preparation on postoperative pain
12. Lack of knowledge and skills in the use of psychological strategies in pain management
13. Use of the "prn" regimen and failure to use around-the-clock dosing schedules
14. Knowledge of analgesics more a reflection of the pharmaceutical representative's promotion rather than true knowledge

Attitudes

1. Overconcern about the development of addiction and tolerance
2. Overconcern about respiratory depression
3. Complete pain relief not the goal of analgesic therapy
4. Belief that some pain is good for the patient
5. Not believing patients can responsibly self-administer their analgesic medications
6. Fear that relieving pain may mask symptoms of underlying pathologic processes
7. Belief that patients are not really in pain, but just trying to get narcotic medications
8. Failure to recognize that pain is more than just a neural process; that it is a human experience of suffering
9. Not viewing adequate pain relief as a priority of medical care
10. Discrepancy between patient's rating of pain and the caregivers' rating of pain
11. Belief that if the patient really has pain there will be concomitant physiological signs
12. Unrelieved pain is too readily accepted by the caregivers
13. Caregivers are held responsible for tasks completed, not for adequacy of pain control
14. Need for the patient to please the physician and nurses and not be viewed as a "problem patient"
15. Reluctance of nurses to contact physicians if pain control is inadequate
16. Race, sex, and medical funding may influence decisions on how to medicate patients

Systemic factors

1. Assignment of a low priority to pain management
2. Lack of auditing of adequacy of pain control by the accrediting agencies
3. Inadequate dissemination of modern pain control methods such as patient-controlled analgesia
4. Restraint of where certain analgesic techniques can be used, for example, restriction of spinal opiate therapy to intensive care units
5. Even simple pain relief techniques require ad hoc physician approval
6. Pain control relegated to the least trained member of the health care team
7. Inadequate teaching of pain management in medical, nursing, and pharmacy schools
8. Lack of specialized pain management services
9. House staff learn the beliefs of their seniors rather than from authorities

Table 1. (*Continued*)

Systemic factors (*continued*)
10. Lack of thorough and frequent re-evaluation of the effectiveness of pain control interventions
11. Inadequate guidelines for nurses to titrate analgesic medications
12. Medical, surgical, and nursing textbooks contain a paucity of information on pain management
13. Subspecialization tends to fragment care, yet more knowledgeable members of the health care team may not have responsibility for pain relief and patient care
14. Lack of pain control studies in community medical care facilities to demonstrate what is possible outside of university-based medical centers

Resultant behaviors or consequences
1. Physicians order analgesic doses too small with dosage intervals too long
2. Analgesic orders written "prn" rather than on fixed interval dosing
3. Dosage range and "prn" dosing interpreted to mean "as little as possible, as infrequently as possible"
4. Patients fear being thought of as complainers, so do not ask for medication to relieve their pain
5. Delays in dosing due to postsurgical units' staffing patterns
6. Increased dosages to prolong effect that results in the increased side effects of sedation and respiratory depression
7. Inadequate reassessment of effects of analgesic interventions
8. Patients fear addiction to opiate analgesics, so they do not request as much medication as needed to effectively relieve their pain
9. Unrelieved pain prevents adequate pulmonary, toilet, ambulation, mobility, and sleep
10. Inadequate sleep leads to fatigue and worse pain control

trolling postoperative pain. The second question that logically follows is why is acute pain left uncontrolled in modern medical practice? To examine the barriers that prevent the effective control of postoperative pain a table of factors that contribute to inadequate treatment of acute pain has been developed. This table is modeled on a matrix developed by the Wisconsin Cancer Pain Initiative.[8] Many of the factors that result in unrelieved cancer pain also impact acute pain control.

There are six persons or elements involved in postoperative analgesic care: the nursing, medical, and pharmacy staffs, the institution or health care system, the drug-regulation system, and most importantly, the patients and their families. Barriers to effective pain control can be classified into three groups: (1) knowledge and skills, (2) attitudes, and (3) systemic factors. These barriers result in behaviors or consequences that contribute to unrelieved pain and the patient's suffering (Table 1).

Not each person or system involved in pain control is subject to all of these barriers and behaviors, but each caregiver, nurse, physician, and pharmacist is subject to many. The health care system perpetuates inadequate pain treatment by not recognizing and eliminating its barriers. The patients and their families; not through any fault of their own, but because of inadequate knowledge, fears, and misguided expectations, settle for less than is their due when they fail to expect, request, and demand adequate relief from acute pain.

SUMMARY

Fifteen years ago it was demonstrated that physicians underprescribed analgesic medications for hospitalized patients. In the intervening years, despite advances in the understanding of the pathophysiology of acute pain, the neural pathways that transmit nociception, and development of new analgesic medications and techniques, the fact remains that many patients suffer from unrelieved acute pain. Motivation is not sufficient to ameliorate this problem. Recognition of the barriers that stand in the way of effective acute pain control are needed. Barriers include physician, nurse, and other caregiver deficits in knowledge and skills, counterproductive attitudes, and health care systemic factors. But recognition of barriers is not enough either. Solutions need to be found so that in 5 or 10 years when studies such as those mentioned are repeated, it is not the finding that patients are underprescribed, undermedicated, and unrelieved of their acute pain.

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Pain Pathways and Spinal Modulation

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Pain, under normal circumstances, results from activation of nociceptors in the periphery. This is indicative of potential or actual tissue destruction. Pain perception can be divided into two components: (1) the sensory-discriminative aspect that describes the location and quality of the stimulus, and (2) the motivational-affective portion that leads to the aversive aspect of pain.[57] Within the CNS, the pathways responsible for these two components of pain become anatomically distinct.[72]

PRIMARY AFFERENT FIBERS

Nociceptors are unencapsulated or "free" nerve endings that discharge when noxious levels of mechanical, thermal, or chemical stimuli threaten or produce damage. They are supplied by a subpopulation of the small diameter myelinated (Aδ) and unmyelinated (C) nerve fibers, which transmit the information to the spinal cord. Activation of the Aδ fibers produces a short-lasting pricking pain, whereas activation of only the C fibers produces a poorly localized burning sensation.[90, 91]

Pain sensation is dependant on the particular afferent fibers being activated (labeled line) and not on the pattern of stimulation. This has been demonstrated in awake humans by recording from individual peripheral nerve fibers using microneurography and determining the fibers' receptive fields and the type(s) of stimulation that activates them. These same fibers are then stimulated electrically through the microelectrode. Stimulation of only those fibers connected to nociceptors produces a sensation of pain.[51, 90] Stimulation of other fibers at the same or even higher frequencies results in sensations appropriate to their receptors,[81, 94] but never pain. Many of these fibers

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contain a variety of neuropeptides and excitatory amino acids.[55, 85] Administration of noxious, but not innocuous levels of stimulation to the tissue or nerves has been shown to induce selective release of neurotransmitters into the spinal cord in several animal models.[9, 33, 52] There appears to be some correlation between the type of noxious stimulus used to induce pain and the particular agent released into the cord. Increased levels of substance P (SP) release into the spinal cord follows application of noxious levels of either heat or mechanical stimuli[9, 22] to the skin. In contrast, although somatostatin release has also been demonstrated with heat input, painful pinch or squeezing fails to elicit somatostatin release.[52] However, Snow and colleagues[55] found no pattern at all between the modality that activates a fiber and the immunoreactive substances found within it. Intrathecal injection of SP in rodents appears to be highly noxious and leads to biting and scratching directed at the hind limbs.[30, 99]

The small primary afferents enter the spinal cord primarily in the lateral portion of the dorsal root, then bifurcate into both rostral and caudal branches. These travel within Lissauer's tract. It is noteworthy that a significant fraction of the unmyelinated C (presumably nociceptors) fibers have branches in the ventral root.[15] This has been demonstrated in humans as well as several other species.

Injection of tracing agents such as HRP or Phaseolus lectin into physiologically identified "pain fibers" originating from skin, muscle, and viscera has shown that their terminals are located primarily in the ipsilateral spinal cord. A heavy concentration of nerve terminals are found in Rexed's laminae I, II, and V in the dorsal horn and around the central canal as well as in contralateral lamina V.[56, 87, 88] There are differences in termination depending on the source (skin, muscle, and viscera) and type (Aδ or C) of the fiber. Within the length of the spinal cord, the visceral afferents have the most extensive longitudinal spread, extending for up to 5 segments compared with 1 to 2 segments for the afferents of cutaneous origin.[88] This may partially explain the diffuse quality of visceral pain.

SPINAL CORD

After entry into the spinal cord, the nociceptive signal is relayed, possibly through interneurons, to projection cells for transmission to the brain. Prior to transmission, processing through local circuits and via descending projections occurs to an unknown extent. Electrophysiologic examination of unidentified cells (both interneurons and a variety of projection cells) results in two main categories that respond to noxious stimulation of the periphery; nociceptive specific (NS) and wide dynamic range (WDR) cells. NS cells respond exclusively to noxious stimulation. WDR cells respond to both innocuous and noxious stimuli, but their discharge frequency is correlated with the strength of the input. NS cells are a continuation of the labeled line; a specific pathway used only for signaling pain. Action potentials in them provide an unambiguous message that stimulation of nociceptors has occurred. Discharge of a WDR cell must be interpreted as to frequency and pattern or processed stimultaneously with other information before the nature of the stimulus is perceived.

Concentrations of these two cell types are found in lamina I (predominantly NS) and lamina V (predominantly WDR) corresponding to the location of nociceptor terminals. Their dendrites extend into other lamina and receive synaptic contacts away from the cell bodies.

Both WDR and NS cells are often selectively excited by iontophoretic application of SP.[40, 76] This excitation may be of long duration, suggesting that SP modulates the excitability of cells rather than acts as a classical neurotransmitter.[93]

FUNICULAR PATHWAYS

Sweet and colleagues[97] have concluded that "the position of the axons (of projection cells) which conduct pain is very variable." This statement is based on a comparison of spinal cord histology with reports of patients concerning their relief from intractable pain after cordotomy. Presumably identical lesions may produce long-lasting elimination of pain in one patient and insignificant or only transient relief in another. Experiences of clinicians with lesions of the cord produced by injury or disease have most strongly associated somatic and visceral pain transmission with the contralateral anterolateral quadrant of the spinal cord.[66] Destruction of fibers crossing the spinal cord by a midline cut produces a bilateral reduction in pain.[41] This also points to a crossed pathway for pain transmission. In addition, stimulation of the anterolateral quadrant in awake patients prior to percutaneous cordotomy results in sensations of contralateral pain. Anterolateral cordotomy is successful in producing immediate, complete pain relief in 70 to 80 per cent of patients.[63, 97, 98] The analgesic region is contralateral to the lesion and usually begins 1 to 2 segments caudal to it, although this may vary. In patients examined a year or more after cordotomy, pain returns in a significant number of cases and the percentage maintaining adequate analgesia drops to about 50 per cent.[63, 97] Lesioning the entire ventral quadrant is more effective than cutting only the anterolateral funiculus.

VENTRAL PATHWAYS

The individual pathways in the anterolateral cord presumed to be responsible for pain transmission are the spinothalamic, spinoreticular, and spinomesencephalic tracts (Fig. 1). Often fibers within one of these pathways contribute collateral axons to the other(s). Cells within the spinothalamic tract (STT) are located throughout the gray matter of the spinal cord. They project to the contralateral thalamus

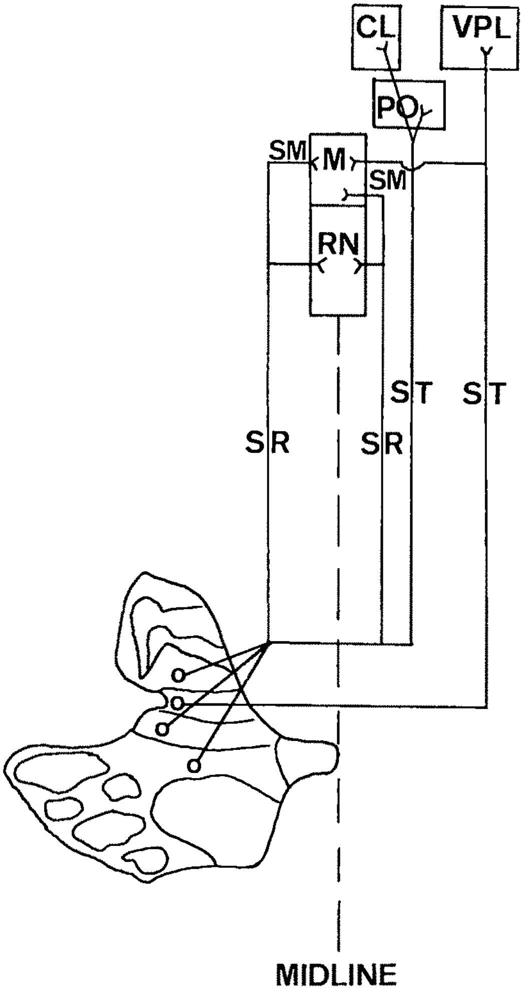

Figure 1. Putative pain pathways in ventrolateral white matter of the spinal cord. Spinothalamic tract (ST) terminations are shown in ventral posterior lateral (VPL), central (CL), and posterior (PO) thalamus. Spinomesencephalic (SM) and spinoreticular (SR) tracts end in the midbrain (M) and the more caudal reticular nuclei (RN), respectively. The SR and SM pathways are both bilateral, although the contralateral projection predominates.

through the ventrolateral funiculus and cross the spinal cord within a short distance of the cell body.[6, 102] Cells projecting laterally to the ventral posterior lateral nucleus of the thalamus (VPL), the major thalamic sensory relay nucleus, are concentrated in the dorsal horn in areas equivalent to lamina V. Cells projecting medially terminate in the intralaminar complex including the central lateral nucleus. The cells of origin are located primarily in laminae IV to VIII.[32] The distributions of these two populations are overlapping, and some cells send collaterals to both thalamic areas. The lateral projection conveys information to the areas SI and SII of the sensory cortex in parallel with other somatosensory pathways. The medial division projects to the frontal, parietal, and limbic regions of the cortex. Thus, this represents the beginning of the clear division between the discriminative and affective components of pain.

The majority of STT cells projecting to the VPL nucleus are presumably involved in nociception. Most are WDR (60 per cent) and NS (32 per cent) cells with a small number responding exclusively to low-intensity or proprioceptive stimuli.[103] The receptive fields of the cells are on the ipsilateral body and in general, are excitatory and of relatively small size. The NS cells tend to have significantly smaller receptive fields than the WDR cells.[104] Many of these cells are inhibited by intense stimulation on other portions of the body. The circuitry of this phenomena involves a supraspinal loop, since high spinal transection eliminates part of this inhibition.[31] The population of STT cells projecting exclusively to the intralaminar complex has a preponderance of NS cells with large, frequently whole body excitatory receptive fields. Many of these cells respond to noxious stimulation with an increase of activity that is of a much longer duration than the stimulus itself. Thus, the cells with well-localized receptive fields feed into the discriminative sensory system and those that signal the presence of pain, if not the specific location, project into a system associated with production of arousal and avoidance.

Throughout the cord some STT cells respond to stimulation of muscle and viscera[29, 60] as well as to skin. Although many cells respond exclusively to cutaneous stimulation, cells responding to just visceral stimulation have not yet been reported. All cells with viscera included in their receptive fields also receive cutaneous input. These neural connections offer one explanation of pain referral.

Spinorecticular tract cells in the primate project both ipsilaterally and contralaterally.[49] Their response properties and receptive field size may resemble STT cells that project either to the VPL thalamus or the intralaminar complex[36]; however, their cells of origin are interspersed with those of the medially projecting STT cells. They terminate primarily in the more medial of the reticular nuclei. Spinomesencephalic (SM) cells also frequently have extended excitatory receptive fields with complex inhibitory input from skin, muscle, and viscera.[110] The cells of origin are located in the same part of the cord as the VPL projecting cells, although there is a stronger ipsilateral projection than that found for the STT population.[109] When these cells also send a collateral to the VPL thalamus the cell has characteristics more typical of those projecting solely to the VPL than of those that project only to the midbrain.[110]

DORSAL PATHWAYS

However, transecting the fibers in the anterolateral cord does not always relieve pain. Often after a successful cordotomy, pain returns after a matter of weeks or months; thus, there must be other pathways capable of mediating pain transmission.

Additionally, intense stimulation can sometimes break through

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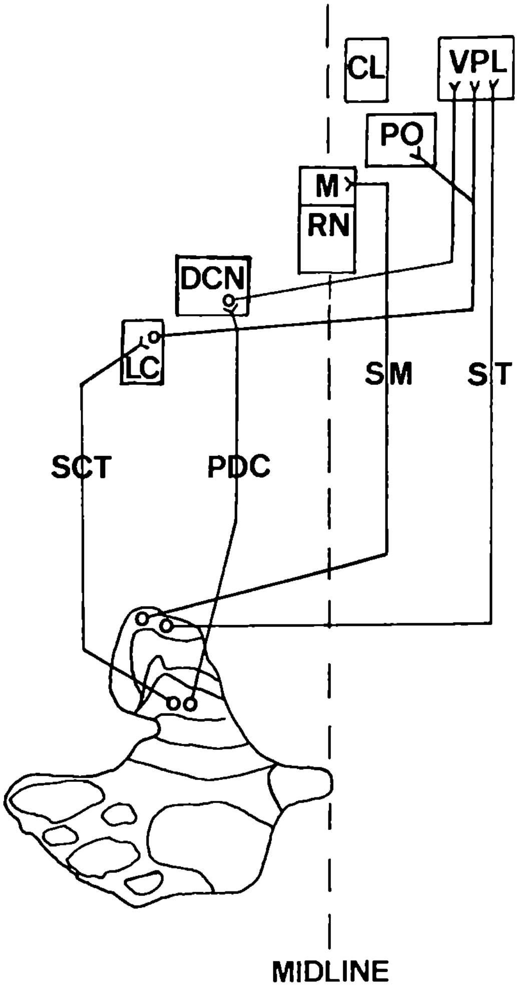

Figure 2. Organization of pathways carrying nociceptive information in the dorsal spinal cord. Lamina I spinothalamic tract (ST) cells terminate in the ventral posterior lateral (VPL) and posterior (PO) thalamic nuclei. Other projections to VPL include the postsynaptic dorsal column (PDC) pathway which synapses in the dorsal column nuclei (DCN) and the spinocervical tract (SCT) which synapses in the lateral cervical (LC) nucleus. A fourth dorsal tract, the spinomesencephalic tract (SM), goes from lamina I to the midbrain (M). CL = central thalamus; RN = reticular nuclei.

the analgesia. This indicates that the analgesia might more correctly be called an increase in threshold. This clinical observation has been replicated experimentally in the primate.[96] After unilateral cordotomy, the animal's response to pain always recovered over time. Even after bilateral section of the ventrolateral and ventral columns, some response to noxious levels of stimulation returned after several months.

There are fiber tracts projecting through the dorsal half of the spinal cord with NS and WDR cells of origin equivalent to those seen in the ventral tracts. These pathways probably also contribute to the pain experience and may take on some of the function of the ventral pathways after their injury. These alternate dorsal pathways (Fig. 2) include the STT and SM projections from lamina I, the spinocervicothalamic pathway, and the postsynaptic dorsal column pathway.

Lamina I contains both NS and WDR cells that project to the VPL thalamus and the mesencephalon.[25] The axons of these cells appear to travel in the dorsolateral fasciculus (DLF) rather than in the ventrolateral quadrant.[43, 46] In the primate, a higher percentage of these cells are NS than are found in the ventral STT projection and the receptive fields of the cells tend to be smaller.[25] Cells of origin of the spinocervical tract are concentrated in lamina IV, and they project to the ipsilateral lateral cervical nucleus (LCN) via the DLF. This nucleus lies ventrolateral to the dorsal horn of the C_1 to rostral C_3 spinal segments. The pathway continues to the contralateral VPL nucleus of the thalamus.[7, 20] Its importance in pain transmission is unknown. The size of the LCN shows great variability in man, frequently being so small that it is hard to detect in postmortum histology.[50] In monkeys, 55 per cent of LCN cells code for painful input in contrast to 92 per cent for the ventral projecting STT cells and all lamina I STT cells.[20, 103] A third dorsal pathway contains cell bodies in lamina IV that project ipsilaterally within the deep dorsal columns to nucleus gracilus and cuneatus in the brainstem.[2, 3, 79] Cells in the dorsal column nuclei (DCN) also project to the VPL thalamus; however, it is unclear how much of the nociceptive input to the DCN is relayed on to the thalamus. Little investigation of this pathway has been done in the primate.[24]

SPINAL MODULATION OF PAIN

Pain can be alleviated at the spinal cord level by (1) blockade of the receptors of the neurotransmitters released by the small diameter primary afferent fibers; (2) inhibiting the release of these neurotransmitters; or (3) "jamming" the processing or transmission of the nociceptive information within the dorsal horn. Either of these last two mechanisms may be achieved through activation of descending or intrinsic elements of the endogenous analgesia system.

Thus far, antagonists to only one primary afferent neurotransmitter have been infused into the spinal cord of awake behaving animals. D-amino acid substituted forms of SP given intrathecally to rodents alter their nociceptive threshold.[68, 70, 95] However, these antagonists also act as partial agonists. In addition, the dose range required for analgesia is just slightly less than that which produces a temporary flaccid paralysis.[68] This renders it unsuitable for clinical use. Increases in the dose lead to a permanent loss of motor function and histologic examination of the spinal cord shows extensive necrosis of cell bodies in both the ventral and dorsal horns.[70] Measurements of blood flow after administration of SP antagonists suggests that the necrosis may be secondary to spinal ischemia.[35]

Of particular interest is the fact that opiate receptors (mu and delta with a higher percentage of mu receptors) appear to be located on the primary afferent fibers.[27] Prior administration of opiates decreases the release of SP after high-intensity stimulation of nerves.[33, 45] Additionally, after dorsal rhizotomy, opiate receptors decrease by about half.[54] Together this indicates that a portion of the opiate effect is likely to be owing to presynaptic inhibition of nociceptive primary afferent fibers. This represents the first site at which the pain message is modified, both endogenously and clinically.

Electrophysiologic studies have shown that iontophoretic application of several putative neurotransmitters alters the response of dorsal horn cells to noxious stimulation. In addition to opiates; 5HT, NE, DA, GABA, Gly, and ACh inhibit the evoked response of nociceptive cells.[23, 28, 42, 100] However, in other experiments, application of many of these neurotransmitters occasionally causes excitation of dorsal horn cells. This discrepancy may be because of individual cell differences or the part of the cell (soma or dendrites) accessed by the drug.[21]

The spinal actions and interactions of 5HT and NE have been studied in depth. Both monoamines are contained within pathways originating in the brainstem and descending in the lateral funiculi[8, 10] to the spinal cord. Chemical lesions of either the serotonergic or noradrenergic system lower the animals' threshold to painful input (hyperalgesia).[75, 108] This is consistent with the idea that tonically active serotonergic and noradrenergic pathways are involved in the processing of nociceptive information within the spinal cord.

Serotonergic Modulation

The presumed sources of the 5HT involved in endogenous analgesia systems are the raphe nuclei. Approximately 80 per cent of the descending raphe fibers contain serotonin.[8] Direct stimulation of n raphe magnus of the DLF evokes release of 5HT in the spinal cord.[37, 86] Electrical stimulation within raphe magnus raises the thresholds of nocifensive (aimed at avoiding noxious stimuli) reflexes.[67, 74, 76, 101] Experiments have indicated that activation of the raphe-spinal system may selectively reduce the response of pain transmission cells to high-intensity input, while either not inhibiting or only slightly reducing the cell's response to low-intensity stimuli.[4, 38] Lesion of the n raphe magnus lowers the stimulation threshold required for an animal to emit a reflex response associated with pain perception.[73] Lesion of any one of several raphe nuclei reduces the antinociceptive effects of systemic morphine.[74, 107]

Intrathecal administration of 5HT or its agonists raises the nociceptive threshold in a manner similar to raphe magnus stimulation.[19, 108, 112] This analgesia occurs in the absence of motor system side effects, although greatly increased levels of 5HT do cause tremor and a mild myoclonus.[108] The analgesia is thought to be the product of a postsynaptic inhibitory action, since 5HT has been shown to inhibit the response of nociceptive dorsal horn cells to iontophoretically applied SP.[40, 76] Indeed, there seems to be a positive correlation between SP's ability to excite a cell and whether or not 5HT inhibits it.[40]

Intrathecal administration of 5HT antagonists causes hyperalgesia in most instances,[108] but has been reported to have no effect in others. Pretreatment with antagonists prevents or reduces analgesia produced by activation of cells in the raphe magnus as well as that induced by intrathecal 5HT.[47] Depleting serotonin by feeding rats a tryptophan-free diet results in hypersensitivity and a reduced effectiveness of morphine.[82] There is a great deal of controversy in regard to the interactions of the serotonergic system with the systemic actions of morphine; the most common finding is that depletion of 5HT is associated with a reduced effectiveness of morphine. Increasing the availability of 5HT is commonly thought to potentiate the actions of morphine,[16] although, again, this opinion is not unanimous. Intrathecal administration of naloxone has recently been shown to reduce the effectiveness of intrathecal 5HT.[48]

Interestingly, the integrity of the noradrenergic system seems to be necessary for the serotonergic system to work. Depletion of norepinephrine (NE) or blockade of α-adrenergic terminals causes a decrease or elimination of the hypoalgesia caused by intrathecal 5HT or raphe magnus stimulation.[69] The converse, however, is not true. The integrity of the 5HT system has not been seen to have an effect on spinal α-adrenergic analgesia.

Noradrenergic Modulation

Catecholamine-containing cells project to the spinal cord from several brainstem sites, most notably the locus coeruleus-subcoeruleus complex, lateral reticular nucleus, and the magnocellular region of the reticular formation. Stimulation of these supraspinal sites has been shown to release NE in the spinal cord, inhibit responses of dorsal horn neurons to noxious stimulation and produce inhibition of nocifensive reflexes.[11, 37, 47] Lesions of these brainstem nuclei have been shown initially to produce hypoalgesia and also to interfere with morphine analgesia.[5] After 1 week to 10 days, a hypersensitivity to NE develops, the hypoalgesia disappears, but the animal is more sensitive to NE and to morphine.[4, 44, 71] However, reserpine and other NE-depleting agents reduce the effectiveness of morphine.[39] Intrathecal administration of norepinephrine also elevates the nociceptive threshold.[23, 59, 77] Analgesia produced by both supraspinal stimulation and intrathecal NE appears to be mediated by an α-adrenergic receptor.[47, 77] Motor effects (hindquarter weakness) do not occur until 20 times the effective analgesic dose of intrathecal NE has been given.[77] The α-2 receptor is thought to make the greatest contribution to this effect (however, see Kellstein et al). Beta-adrenergic receptors are not involved. Intrathecally administered antagonists cause hypoalgesia; α-2 agents are more effective than α-1. Administration of α-2, but not α-1, antagonists interferes with morphine analgesia.[80]

As is the case for 5HT, the analgesia is dose dependant; however, unlike 5HT, pretreatment with naloxone does not block NE-induced analgesia.[77] The analgesia is not antagonized by local administration of vasodilator agents, indicating that the changes are not due to a local ischemia. Nor is it mimicked by intrathecal vasoconstrictors.[77, 108]

Iontophoretically applied NE inhibits the responses of dorsal horn neurons to noxious stimulation and facilitates their responses to innocuous stimulation.[42] NE has been reported to inhibit noxious stimulation induced release of SP, indicating a possible presynaptic as well as postsynaptic inhibitory role. This presynaptic inhibition also appears to be mediated by the α-2 receptor.[53,62]

Clonidine, an α-2 agonist, has been shown to raise nociceptive thresholds when injected intrathecally in animals. Epidural and intrathecal clonidine are used clinically to provide pain relief in humans.[17] When used in combination with opiates there appears to be a synergy that extends the duration and magnitude of relief. Combination therapy also delays the development of tachyphylaxis or tolerance to either drug. Intrathecal clonidine is an effective analgesic in animals and patients who are morphine tolerant. Indeed, in both animal and human subjects, clonidine has been shown to halt many of the side effects of morphine withdrawal.[1, 26, 34]

The analgesic effects of both 5HT, NE and their agonists are potentiated by prior administration of monoamine oxidase inhibitors and monoamine reuptake inhibitors. Both types of agents increase extracellular concentrations of 5HT and NE in the spinal cord and thus raise pain thresholds.[108] There are several clinically relevant examples of this. Tricyclic antidepressants are known to relieve pain apart from their antidepressant action. This could be due to their ability to function as potent monoamine reuptake blockers.[89] Ester local anesthetics are monoamine oxidase inhibitors; amide local anesthetics are not. Tetracaine (an ester) also inhibits the uptake of NE into synaptosomes. Thus, ester local anesthetics may act to increase available NE by two simultaneous mechanisms.[78] Interestingly, both monoamine oxidase inhibitors and reuptake inhibitors also potentiate morphine analgesia.[18] This potentiation is blocked by administration of either serotonergic or α-adrenergic receptor blockers.

Somatostatin Modulation

Somatostatin is a putative primary afferent neurotransmitter. Ionophoretic application of somatostatin, like NE, selectively inhibits dorsal horn cells that respond to noxious stimulation and excites or has no effect on those that respond exclusively to low-threshold input.[76] This could make it a candidate for administration as an intrathecal analgesic agent. In addition, intrathecal injection of somatostatin in rats leads to caudally directed biting, writhing, and retching.[84] In anesthetized animals, somatostatin causes a facilitation of a nocifensive flexion indicative of a heightened response to a given input. Histologic examination of spinal tissue after a low dose of somatostatin reveals no damage. Intrathecal injection of high-dose somatostatin in rats leads to hindlimb flaccidity, hemodynamic changes, and frequently loss of the micturation reflex.[105] Examination of the spinal cord tissue shows inflammation and loss of cells in both ventral and dorsal horns.[105] Intrathecal somatostatin has been given in humans for both acute and chronic pain.[12–14, 58] One advantage seems to be a lack of cross tolerance with morphine. Reported side effects include nausea and mild hypoglycemia. However, the total lack of human postmortum histology is a serious concern given that somatostatin causes necrosis of spinal cells in rodents. More animal studies should be performed to ascertain if this toxicity is species specific or a common reaction. Recent data have been published indicating a possible link between somatostatin and augmentation of gastric cancer cell growth.[61] Clinical use of spinal somatostatin should be reconsidered and limited to the terminally ill until further investigations confirm or refute these potential dangers.

SUMMARY

Specific pain pathways transmit information regarding actual or impending tissue damage. In the spinal cord, several parallel pathways serve this function. Endogenous descending systems modulate pain transmission and ultimately pain perception. Natural neurochemicals and their analogues are being found that selectively inhibit pain and do not alter transmission of other sensory information.

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Clinical Pharmacology of Opioid Analgesics

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In a now classic 1973 survey, Marks and Sachar[24] documented that most hospitalized patients with moderate to severe pain receive inadequate doses of opioids. The physicians surveyed underestimated the patients' intensity of pain and overestimated the duration of analgesic action of the dose of opioid they prescribed. In addition, they overestimated the risk of opioid abuse or addiction in a medical population. Since 1973 a number of innovative approaches to opioid drug delivery have increased the utility of opioids and major educational efforts by individuals, and pain societies have increased awareness of the problem and resulted in significant progress. However, a recent survey[7] indicates many medical-surgical patients with pain continue to receive inadequate doses of analgesics so that much more needs to be accomplished before this significant health care problem can be considered to be under control. The effective use of analgesic drugs is derived from a full assessment of the type of pain, acute versus chronic, the definition of the specific pain syndrome, and an understanding of the clinical pharmacology of the drug to be prescribed.[14] Although postoperative pain is commonly considered to be resolved after 3 to 4 days, Melzack et al[25] found that a substantial proportion, that is, 31 per cent of patients in a surgery ward, had pain that persisted for more than 4 days after surgery owing to infection or other medical complications. Thus, the appropriate management of both acute and persistent pain should be part of every physician's armamentarium. The purpose of this article is to discuss the pharmacologic principles and properties of the opioid analgesics in the management of pain. Particular emphasis is placed on the selection and use of these drugs for the relief of moderate to severe acute, postoperative pain.

The fundamental concept that underlies the appropriate and successful management of pain, regardless of duration or intensity, is individualization of analgesic therapy.[31, 33, 39] This concept entails selection of the right analgesic, administered in the right dose, on the

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Table 1. *Opioid Analgesics Commonly Used for Severe Pain*

NAME	ROUTE	EQUIANALGESIC DOSE* (MG)	PEAK† (HR)	DURATION (HR)	COMMENTS	PRECAUTIONS
Morphine-like agonists						
Morphine	IM	10	½–1	4–6	Standard of comparison for opioid analgesics	Lower doses for aged patients, impaired ventilation; bronchial asthma; increased intracranial pressure; liver failure
	PO	60‡	1½–2	4–7		
Meperidine (Demerol)	IM	75	½–1	4–5	Slightly shorter acting, used orally for less severe pain	Normeperidine (toxic metabolite) accumulates with repetitive dosing causing CNS excitation; not for patients with impaired renal function or receiving monoamine oxidase inhibitors‖
	PO	300§	1–2	4–6		
Methadone (Dolophine)	IM	10	Like IM morphine		Good oral potency, long plasma half-life	Like morphine; may accumulate with repetitive dosing causing excessive sedation
	PO	20	Like PO morphine			
Levorphanol (Levo-Dromoran)	IM	2	Like IM morphine		Like methadone	Like methadone
	PO	4	Like PO morphine			
Heroin	IM	5	½–1	4–5	Slightly shorter acting; biotransformed to active metabolites (eg, morphine); not available US	Like morphine
	PO	(60)§	Like PO morphine			
Hydromorphone (Dilaudid)	IM	1.5	Like IM heroin		Slightly shorter acting	Like morphine
	PO	7.5	Like PO morphine			
Oxymorphone (Numorphan)	IM	1	Like IM morphine		Like morphine	Like morphine

Codeine	IM	130	Like IM morphine		Like morphine, used orally for less severe pain	Like morphine
	PO	200				
Mixed agonist-antagonists						
Pentazocine (Talwin)	IM	60	Like IM morphine		Used orally for less severe pain; mixed agonist-antagonist; less abuse liability than morphine; included in Schedule IV of Controlled Substances Act	May cause psychotomimetic effects; may precipitate withdrawal in opioid-dependent patients, not for myocardial infarction‖
	PO	180§	Like PO morphine			
Nalbuphine (Nubain)	IM	10	Like IM morphine		Not available orally; like IM pentazocine but not Scheduled	Incidence of psychotomimetic effects lower than with pentazocine
Butorphanol (Stadol)	IM	2	Like IM morphine		Not available orally like IM nalbuphine	Like IM pentazocine
Partial agonists						
Buprenorphine (Buprenex)	IM	0.4	Like IM morphine		Not available orally; sublingual preparation not yet available in US; less abuse liability than morphine, does not produce psychotomimetic effects	May precipitate withdrawal in opioid-dependent patients
	SL	0.8	2–3	5–6		

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* These doses are recommended starting doses from which the optimal dose for each patient is determined by titration and the maximal dose limited by adverse effects.

† Peak time and duration of analgesia are based on mean values and refer to the stated equianalgesic doses in nontolerant patients.

‡ A value of 3 is used when calculating an oral dosage regimen of every 4 hours around the clock.

§ Not recommended.

‖ Irritaing to tissues on repeated administration.

Modified from Inturrisi CE, Foley KM: Analgesics: Neurochemical, Behavorial and Clinical Perspectives. New York, Raven Press, 1984, p 257.

right schedule so as to maximize pain relief and minimize adverse effects. Its practical application requires, for example, recognition of the different pharmacologic profiles that exist among the opioid analgesics, the abandonment of the standard, fixed dose approach, and its replacement with a willingness to titrate the recommending starting analgesic dose (Table 1) up or down as required by each patient.

OPIOID ANALGESICS: THEIR SOURCES AND SITES OF ACTION

Opioids vary in their interactions with multiple opioid receptors and this results in different pharmacologic profiles among the opioids.[18, 28] Both in-vivo pharmacologic studies and in-vitro binding studies indicate the existence of at least eight types of opioid receptors with subtypes of each of these receptors.[28] Certain pharmacologic effects can be related to binding at particular receptors. For example, analgesia has been associated with both mu and kappa receptors, while dysphoria and psychotomimetic effects have been ascribed to sigma and perhaps to kappa receptors.[18] The identification of delta opioid receptors in the limbic region of the brain has led to the suggestion that these receptors may mediate alterations in affective behavior.[18] Although clearly an oversimplification, Table 2 compares the types of interactions of selected opioids at mu and kappa receptors. Morphine is an agonist at both mu and kappa receptors, and activation of these receptors results in analgesia. At the other end of the pharmacodynamic spectrum are the opioid antagonists such as naloxone, which bind to both mu and kappa opioid receptors without activating the systems required for analgesia. Because the antagonist can bind to these receptors but lacks intrinsic activity, it can displace opioid agonists such as morphine from receptor sites and block or reverse the pharmacodynamic effects of the agonist. A mixed agonist-antagonist, for example, pentazocine (Table 2), can bind to both mu and kappa receptors, but the result of these interactions differs dramatically. Pentazocine acts as an antagonist at the mu receptor and agonist at the kappa receptor. Thus, the mixed agonist-antagonist opioids have

Table 2. *Actions of Prototypical Opioids at Their Receptors*

OPIOID	MU	KAPPA
Morphine	Agonist	Agonist
Naloxone	Antagonist	Antagonist
Pentazocine	Antagonist	Agonist
Buprenorphine	Partial agonist	—

Modified from Jaffe JH, Martin WR: The Pharmacological Basis of Therapeutics, ed 7. New York, Macmillan, 1985, p 491.

the potential to act as agonists or antagonists and, depending on the drug and patient circumstances (see following), one of these very different types of pharmacodynamic effects will predominate.

Buprenorphine (Table 2), which binds to the mu receptor, produces analgesia and other CNS effects that are qualitatively similar to those of morphine. However, in receptor-binding studies and in animal studies it can also exhibit antagonist activity.[18] This type of profile is characteristic of a partial or limited agonist (see following).

Morphine-Like Agonists

Morphine is the prototype and standard of comparison for opioid analgesics. The morphine-like agonists (Table 1) share with morphine a similar profile of pharmacodynamic effects both desirable and undesirable. However, they differ in factors critical in dosage selection, that is, relative analgesic potency and oral to parenteral (IM/PO) analgesic potency. They also differ in pharmacokinetics (for example, elimination half-life) and biotransformation to pharmacologically active metabolites.[9, 11, 14] These latter characteristics are of particular importance when opioid administration is continued beyond 1 or 2 days. Much of this information is summarized in Table 1. This dosage information is, for the most part, derived from controlled clinical trials employing single-dose comparisons of opioids to morphine.[10]

Morphine has a plasma elimination half-life in the range of 2 to 3.5 hours, which is shorter than its average duration of analgesia (4 to 6 hours), so that accumulation is usually limited when dosing is scheduled no more frequently than every 4 hours. Furthermore, with repetitive administration its pharmacokinetics remain linear and there does not appear to be autoinduction of biotransformation even following large chronic doses.[35] These pharmacokinetic properties contribute to the safe use of morphine. However, recent studies suggest that impaired renal function may result in the accumulation in plasma of morphine-6-glucuronide, an active metabolite of morphine.[27, 36] The role, if any, of morphine-6-glucuronide in the therapeutic and toxic effects of morphine awaits more definitive studies in patients.

Based on single-dose studies in patients with either acute or chronic pain the relative potency of intramuscular to oral morphine is 1:6.[10] However, with repeated administration, when patients are dosed on a regular schedule (around the clock), the IM/PO ratio is reduced to 1:2 or 1:3.[20] Thus, for patients with acute pain who are being titrated using an as-needed (prn) schedule, the 1:6 ratio should be used with a lower ratio expected, if dosing continues and a steady-state develops.

Table 1 lists other morphine-like agonists that may be substituted for morphine. An alternative opioid to morphine may be selected based on the need with a particular patient to overcome an adverse effect of morphine (for example, vomiting or sedation), considerations of convenience, which may include the patient's favorable prior experience with another opioid or even local availability of other morphine-like opioids. It must be emphasized that there is no evidence to suggest that any opioid has greater analgesic efficacy than morphine.

Given intramuscularly, morphine's analgesic effects peak on the average in ½ to 1 hour and have an average duration of 4 to 6 hours (Table 1). When comparing other opioids, it should be remembered that a variety of factors will result in substantial interindividual variation in the peak and duration of the analgesic effect of an opioid.[14] Nevertheless, in general, methadone, levorphanol, oxymorphone, and codeine have similar analgesic time-action curves to that of morphine, whereas hydromorphone, heroin, and meperidine are slightly shorter acting.

Hydromorphone is a short half-life opioid used as an alternate to morphine in postoperative pain. Also, it is more soluble than morphine and available in a concentrated dosage form at 10 mg per ml (see Table 1). This preparation is intended for parenteral administration to the opioid-tolerant, cachectic patient where the volume of the opioid solution to be injected must be limited. In this regard hydromorphone serves the same role in cancer pain management in the United States as does heroin in those countries where it is available (see following).

Methadone and levorphanol are long half-life opioids that are useful alternatives to morphine. However, when used on a repetitive dosing schedule, they must be titrated carefully, particularly in the opioid-naive patient. Sedation, confusion, and even death can occur when patients are given fixed repetitive doses of methadone during the accumulation period that can last from 5 to 10 days.[8, 9, 12] The safe and effective use of long half-life opioids requires prn scheduling (usually), careful monitoring, and dose adjustment during the accumulation period. After this period a regular schedule can be safely adapted. Both methadone and levorphanol have favorable IM/PO potency ratios (see Table 1).

Oxymorphone is most often used in suppository form and is not available in an oral dosage form.

Meperidine is a widely used analgesic employed predominantly for acute pain. The use of meperidine in IM doses of 250 mg per day or less for short duration in hospitalized patients with normal renal function is not associated with a high incidence of toxicity.[16] However, chronic administration of increasing doses of meperidine results in the accumulation, particularly in patients with compromised renal function, of normeperidine, a metabolite that produces CNS hyperexcitability.[21] In contradistinction, an acute toxic effect characterized by excitation, hyperpyrexia, convulsions, and death has been reported following the administration of meperidine to patients being treated with a monoamine oxidase inhibitor.[16] The pharmacokinetics and mechanisms of this acute, toxic interaction are not understood.

Heroin is a morphine-like opioid. Much controversy has surrounded attempts to make heroin available for use in terminal cancer patients in the United States. Claims for the superior efficacy of heroin over other morphine-like drugs are unsubstantiated. In a single-dose analgesic assay in postoperative patients Kaiko et al[22] found that while intramuscular heroin differs somewhat from morphine with respect to its relative analgesic potency and time-action characteristics (see Table 1), there is no evidence that heroin has any advantages over morphine or other opioids in terms of the occurrence of side effects or the degree of mood improvement at equianalgesic doses.[22] Recent studies in patients and animals support and extend these conclusions.[15] Heroin itself does not bind to the opioid receptor but must be biotransformed to 6-acetylmorphine and morphine to produce its analgesic effect.[15] Therefore, heroin is classified as a prodrug. Following oral administration of heroin, only morphine can be measured in the patient's blood. Thus, use of oral heroin is an inefficient way of delivering morphine to the systemic circulation.[15] Heroin is more soluble than morphine, offering a potential advantage over morphine in the very tolerant patient who requires opioid administration via the parenteral route. However, this advantage of morphine is shared by hydromorphone, an opioid that is more potent and more soluble than heroin. Furthermore, the use of subcutaneous infusion of available opioids often obviates the need to administer large and repeated parenteral bolus doses to the tolerant patient.

Fentanyl is a mu opioid agonist. It has not been subjected to a definitive relative potency assay, and therefore is not listed in Table 1. However, fentanyl is estimated to be approximately 80 times as potent as morphine.[18] It is a highly lipophilic drug with shorter duration of action than parenteral morphine. Fentanyl is used for the management of postoperative pain by the intravenous[1] and epidural[5] routes of administration and its delivery from a transdermal patch device is currently under development.[3]

Agonist-Antagonist Analgesics

The mixed agonist-antagonist analgesics (see Table 1) include pentazocine, butorphanol, and nalbuphine. They produce analgesia in the nontolerant patient presumably by acting as agonists at the kappa receptor (see Table 2), but will precipitate withdrawal in patients tolerant to morphine-like drugs by acting as an antagonist and displacing the morphine-like opioids from the mu receptor. Therefore, when used for chronic pain they should be tried before the repeated administration of a morphine-like agonist drug. There is a ceiling effect on the ability of the mixed agonist-antagonists to produce respiratory depression and they have a significantly lower abuse liability than the morphine-like drugs. In therapeutic doses, they may produce certain self-limiting psychotomimetic effects in some patients, with pentazocine, the most common drug associated with these effects.[9] Nalbuphine and butorphanol are currently only available for parenteral use and the oral preparation of pentazocine is marketed in combination with naloxone.

Partial Agonist Analgesics

The partial agonist buprenorphine (see Table 1) has less abuse liability than the morphine-like drugs but like the mixed agonist-antagonists, it may also precipitate withdrawal in patients who have received repeated doses of a morphine-like agonist and developed physical dependence. Withdrawal is believed to result when buprenorphine, a "partial" agonist, replaces a "full" morphine-like agonist at mu receptors. Buprenorphine does not produce the psychotomimetic effects seen with the mixed agonist-antagonists and is available in both a sublingual and parenteral form. Only the latter dosage form is currently available in the United States. Buprenorphine's respiratory depressant effects are not reversed by naloxone, making it a drug whose use must be undertaken cautiously.

OPIOID PHARMACOKINETICS

As noted previously, the opioids differ significantly in one measure of drug elimination, the plasma half-life value (Table 3). So that while morphine and hydromorphone are short half-life opioids that on repeated dosing reach steady-state in 10 to 12 hours, levorphanol and methadone are long half-life opioids that on the average may require 70 to 120 hours, respectively, to achieve steady-state. During dose titration the maximal (peak) effects produced by a change dose of a short half-life opioid will appear relatively quickly while the peak effects resulting from a change in the dose of a long half-life opioid will be achieved after a longer accumulation period. For example, a patient who reports adequate pain relief following the initial doses of methadone may experience excessive sedation if this dosage is fixed and not modified as required during the accumulation period of 5 to

Table 3. *Plasma Half-life Values for Opioids and Their Active Metabolites*

	PLASMA HALF-LIFE (HOURS)
Short half-life opioids	
Morphine	2–3.5
Hydromorphone	2–3
Codeine	3
Meperidine	3–4
Heroin*	0.05
Pentazocine	2–3
Nalbuphine	5
Butorphanol	2.5–3.5
Long half-life opioids	
Methadone	24
Levorphanol	12–16
Propoxyphene	12
Norpropoxyphene	30–40
Normeperidine	14–21

* Biotransformed to acetylmorphine and morphine.

10 days. Opioid pharmacokinetics are altered in patients with cirrhosis or renal disease (see references 9 and 11 for reviews).

INFLUENCE OF AGE ON OPIOID DISPOSITION AND RESPONSE

The clearance of morphine is decreased in individuals over the age of 50, and this age-related difference in pharmacokinetics may explain, in part, the greater sensitivity of older patients to therapeutic doses of morphine compared with younger patients.[9, 19] Other factors play a role, including increased sensitivity of central sites to the therapeutic and adverse effects of these drugs. Thus, the decreased fentanyl and alfentanil dose requirements in the elderly result from age-related changes in pharmacodynamics, that is, increased brain sensitivity to these two opioids rather than pharmacokinetic changes.[37] In practice, reducing the dose or lengthening the time interval between doses for the elderly patient are approaches to minimize the development of serious adverse effects.

The management of pain in children with opioid analgesics follows the same principles as described for the adult patient.[34, 39] The oral and intravenous routes are commonly used to avoid repetitive needle injections. Continuous subcutaneous infusion has been used in the terminally ill child.[26] Individualization of dose and titration to the needs of the child are essential.

ROUTES OF ADMINISTRATION

Intravenous and Intramuscular

Intravenous bolus provides the most rapid onset and shortest duration of action. Time to peak effect correlates with the lipid solubility of the opioid, ranging from 2 to 5 minutes for methadone to 10 to 15 minutes for morphine.[13] Continuous intravenous infusion is used for postoperative pain with dosage controlled by the staff or, in a recent innovation, by the patient as part of a patient-controlled analgesia (PCA) system. PCA is a mode of opioid administration that employs the concept of individualization of analgesic dosage wherein the patients, within limits, can titrate their analgesia requirements. PCA has been widely used for postoperative pain.[38, 41] The intramuscular or subcutaneous routes are commonly used for postoperative pain. Opioids administered by these routes have peak analgesic effects that average 30 to 60 minutes and therefore are slower than after intravenous and more rapid than after oral administration.

Epidural and Intrathecal

These routes are widely used for the management of acute postoperative and obstetric pain.[5] In general, they provide a longer duration of analgesia at doses lower than required by systemic administration. The opioids vary in their distribution in CSF and the rostral redistribution of hydrophilic opioids such as morphine may result in supraspinally mediated adverse effects.[29]

Oral Route

When given orally the opioids differ substantially with respect to their presystemic elimination, that is, the degree to which they are inactivated as they are absorbed from the gastrointestinal tract and pass through the liver into the systemic circulation. As indicated in Table 1, morphine, heroin, hydromorphone, and oxymorphone have ratios of oral to intramuscular potency of 1:5 to 1:12. Methadone, levorphanol, and oxycodone are subject to less presystemic elimination, resulting in an oral to intramuscular potency ratio of at least 1:2. Meperidine and pentazocine have intermediate ratios. The failure to recognize these differences often results in a substantial reduction in analgesia when the change from the parenteral to oral administration is attempted without upward titration of the dose. In general, orally administered drugs have a slower onset of action, delayed peak time, and a longer duration of effect compared with the parenteral route.

Rectal

The rectal route is an alternative to the parenteral route for patients unable to take opioid orally. Rectal suppositories containing hydromorphone, oxymorphone, and morphine are available.

Continuous Subcutaneous Infusion

For patients who cannot absorb adequate amounts of orally administered opioids because of nausea and vomiting, gastrointestinal intolerance, or obstruction, the parenteral routes described previously can be used. However, in addition to circumventing oral absorption, the continuous subcutaneous infusion mode of opioid delivery avoids the problems associated with intramuscular/subcutaneous injection, the need for an intravenous access, and can be used by ambulatory patients. Most opioids available for parenteral use can be administered by continuous subcutaneous infusion. The features and limitations of this mode of opioid administration have been described by Coyle et al.[6]

Other Routes and Modes of Administration

Opioids are currently being evaluated by the transdermal,[3] sublingual,[40] and intranasal[4] routes of administration.

CHANGING THE ROUTE OF ADMINISTRATION

The slower onset of analgesia after oral administration often requires some adaptation on the part of a patient who is accustomed to the more rapid onset seen after a parenteral opioid. The problems associated with switching from the parenteral to the oral route of opioid administration can be minimized by slowly reducing the parenteral dose and increasing the oral dose over a 2- to 3-day period. When patients are switched from the IM to IV or IV to IM route, the assumption is made that the equianalgesic doses by these two routes are the same.[14] However, there are no studies defining the relative potency of opioids by these two routes of administration.

When patients are switched from one opioid analgesic to another or from one route of administration to another, it is the lack of attention to the route-dependent differences in opioid dose that accounts for the common reports of undermedication of patients. In patients who have been receiving one opioid repeatedly to the point where some degree of tolerance has developed and are then switched to another opioid, half of the analgesic drug dose of the new drug should be given as the initial starting dose. This information has been gained empirically but is based on the concept that cross-tolerance is not complete among opioids and conforms to our recognition that the relative potency of some of the opioid analgesics may change with repetitive dosing, particularly those opioids with a long plasma half-life. In using Table 1, it becomes important to recognize that the equianalgesic dose estimates are based on the single-dose studies and they represent a useful reference point for the initiation of dose titration. They are not meant to be used as the standard dose for every patient.

SCHEDULED OPIOID ADMINISTRATION

The schedule of opioid administration should be individualized for each patient. In general, patients with persistent pain should receive opioids on a regular schedule once the patient's dosage has been established by titration using an as-needed (prn) schedule. This approach is especially important when the dose titration involves a long half-life opioid such as methadone or levorphanol, as discussed previously. A regular, around-the-clock schedule of opioid administration can prevent severe pain from recurring and may allow for a reduction in the total opioid required per day. For some patients a prn order for a supplemental opioid dose (rescue) between the regularly scheduled doses may be required to provide adequate pain relief.

DRUG COMBINATIONS THAT ENHANCE ANALGESIA

Drug combinations can provide additive analgesia, may reduce adverse effects, and can reduce the rate of escalation of the opioid portion of the combination.[2, 9] There are several combinations that produce additive analgesic effects. These include an opioid plus a nonopioid, an opioid plus the antihistamine, hydroxyzine, and an opioid plus dextroamphetamine.[2]

ADVERSE EFFECTS OF OPIOIDS

There are a number of adverse effects associated with the use of opioid analgesics that can, depending on the circumstances, be considered as desirable or undesirable effects.[9] It is the development of adverse effects that usually limits the use of analgesics in pain management. The mechanisms that underlie these various adverse effects are only partly understood and appear to depend on a number of factors including the age, extent of disease and organ dysfunction, concurrent administration of certain drugs, prior opioid exposure, and the route of drug administration.[9, 11] The most common adverse effects are sedation, nausea and vomiting, constipation, and respiratory depression. But there are other adverse effects including confusion, hallucinations, nightmares, urinary retention, multifocal myoclonus, dizziness, and dysphoria that have been reported by patients receiving these drugs.

Respiratory Depression

Respiratory depression is potentially the most serious adverse effect. The morphine-like agonists act on brainstem respiratory centers to produce, as a function of dose, increasing respiratory depression to the point of apnea. In man, death due to overdose of a morphine-like agonist is nearly always due to respiratory arrest. Therapeutic doses of morphine may depress all phases of respiratory activity (rate, minute volume, and tidal exchange). However, as Co_2 accumulates, it stimulates the respiratory center resulting in a compensatory increase in respiratory rate that masks the degree of respiratory depression. At equianalgesic doses, the morphine-like agonists produce an equivalent degree of respiratory depression. For these reasons individuals with impaired respiratory function or bronchial asthma are at greater risk of experiencing clinically significant respiratory depression in response to usual doses of these drugs. Respiratory depression and Co_2 retention result in cerebral vasodilation and an increase in cerebrospinal fluid pressure unless PCo_2 is maintained at normal levels by artificial ventilation. When respiratory depression occurs, it is usually in opioid-naive patients following acute administration of an opioid and is associated with other signs of CNS depression including sedation and mental clouding. Tolerance develops rapidly to this effect with repeated drug administration, allowing the opioid analgesics to be used in the management of chronic cancer pain without significant risk of respiratory depression. If respiratory depression occurs, it can be reversed by the appropriate administration of the specific opioid antagonist, naloxone.[9]

Nausea and Vomiting

The opioid analgesics produce nausea and vomiting by an action on the medullary chemoreceptor trigger zone. The incidence of nausea and vomiting is markedly increased in ambulatory patients, suggesting that these drugs also alter vestibular sensitivity. The ability of opioid analgesics to produce nausea and vomiting appears to vary with drug and patient so that some advantage may result from switching to an equianalgesic dose of another opioid. Alternately, an antiemetic may be used in combination with the opioid. For some patients, initiating treatment by the parenteral route and then switching to the oral route may reduce the emetic symptoms.[9]

Sedation

The opioid analgesics produce sedation and drowsiness. While these effects may be useful in certain clinical situations (for example, preanesthesia) they are not usually desirable concomitants of analgesia, particularly in ambulatory patients. The CNS depressant actions of these drugs can be expected to be at least additive with the sedative and respiratory depressant effects of sedative-hypnotics such as alcohol, barbiturates, and benzodiazepines.

A reduction in opioid dose and interval so that a lower dose is given more frequently may sometimes counteract excessive sedation. In addition, other CNS depressants including sedative-hypnotics and antianxiety agents that potentiate the sedative effects of opioids should be discontinued. Concurrent administration of dextroamphetamine in 2.5 to 5.0 mg oral doses twice daily has been reported to reduce the sedative effects of opioids. Tolerance usually develops to the sedative effects of opioid analgesics within the first several days of chronic administration.

Constipation

The most common adverse effect of the opioid analgesics seen with repetitive administration is constipation. These drugs act at multiple sites in the gastrointestinal tract and spinal cord to produce a decrease in intestinal secretions and peristalsis, resulting in a dry stool and constipation. Tolerance develops very slowly to the smooth muscle effects of opioids so that constipation will persist when these drugs are used for chronic pain. At the same time that the use of opioid analgesics are initiated, provision for a regular bowel regimen, including cathartics and stool softeners should be instituted to diminish this adverse effect.

Urinary Retention

Because the opioid analgesics increase smooth muscle tone, they can cause bladder spasm and an increase in sphincter tone leading to urinary retention. This is most common in the elderly patient. Attention should be directed at this potential side effect, and catheterization may be necessary to manage this transient side effect.

THE OPIOID-TOLERANT PATIENT

Tolerance develops when a given dose of an opioid produces a decreasing effect, or when a larger dose is required to maintain the original effect. Tolerance appears to develop in all patients receiving opioid analgesics chronically. The hallmark sign of the development of tolerance is the patient's complaint of a decrease in the duration of effective analgesia. For reasons not yet understood, the rate of development of tolerance varies greatly among patients so that some will demonstrate tolerance within days of initiating opioid therapy while others will remain well controlled for many months on the same dose.[31] A sudden dramatic increase in opioid requirements may represent a progression of the disease (for example, cancer) rather than the development of tolerance per se. In these patients, objective evidence of progression of disease is sought and pain management techniques re-evaluated accordingly.[23]

With the development of tolerance, increasing the frequency or dose of the opioid is required to provide continued pain relief. Because the analgesic effect is a logarithmic function of the dose of opioid, a doubling of the dose may be required to restore full analgesia. The strategies that can be used to maintain pain relief in the tolerant patient have been discussed by Foley and Inturrisi.[9]

THE OPIOID-DEPENDENT PATIENT: DEFINITIONS AND MISCONCEPTIONS

Psychological and Physical Dependence

The properties of the opioid analgesics that are most likely to lead to their being misused, or the patient being mistreated, are effects mediated in the CNS and seen following repeated administration, including psychological dependence and physical dependence. It must be emphasized that although the development of physical dependence and tolerance are predictable pharmacologic effects seen in man and laboratory animals in response to repeated administration of an opioid, these effects are distinct from the behavioral pattern seen in some individuals and described by the terms psychological dependence or addiction.[17] Psychological dependence is used to mean a pattern of drug use characterized by a continued craving for an opioid that is manifest as compulsive drug-seeking behavior leading to an overwhelming involvement with the use and procurement of the drug. Within these definitions anyone who is addicted to opioids is likely to be physically dependent. However, the term addiction cannot be used interchangeably with physical dependence, that is, it is possible to be physically dependent on an opioid analgesic without being addicted. Fear of addition is a major consideration limiting the use of appropriate doses of opioids in hospitalized patients in pain. Some patients are reluctant to take even small doses of opioids for fear of becoming addicted. Surveys in hospitalized medical patients[32] and in burn patients[30] and an analysis of the patterns of drug intake in cancer patients receiving chronic opioids[23] suggest that medical use of opioids rarely, if ever, leads to drug abuse or iatrogenic opioid addiction.

Physical dependence is the term used to describe the phenomenon of withdrawal when an opioid is abruptly discontinued or if an opioid antagonist is administered. The severity of withdrawal is a function of the dose and duration of administration of the opioid just discontinued (that is, the patient's prior opioid exposure). The administration of an opioid antagonist to a physically dependent individual produces an immediate precipitation of the withdrawal syndrome. Patients who have received repeated doses of a morphine-like agonist to the point where they are physically dependent may experience an opioid withdrawal reaction when given a mixed agonist-antagonist. Pain management in the physically dependent patient has been discussed elsewhere.[5]

SUMMARY

It must be emphasized that patients with pain vary greatly in their response to analgesics. Pharmacokinetic factors and pharmacodynamic factors (opioid tolerance, intrinsic sensitivity) as well as psychological factors (pain severity, suffering) will influence the effectiveness of an analgesic in an individual patient. The guidelines, suggestions, and caveats mentioned are intended to facilitate application of the principle of individualization of analgesic dosage so that the therapeutic benefit of analgesics can be maximized while minimizing the adverse effects of these drugs.

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Systemic Opioid Analgesia for Postoperative Pain Management

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> Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium.
>
> SYDENHAM, 1680

We are currently immersed in an international, multidisciplinary drive to improve postoperative pain management. Recent advances in physiology and pharmacology and equipment technology have merged to provide innovative and improved patient care. We are participating in the administration of narcotics into the epidural and intrathecal spaces. We are recommending the use of patient-controlled analgesia (PCA) devices. We are using long-acting opioids (for example, methadone) as anesthetics during surgery with the intent of providing postoperative analgesia.

Traditionally, postoperative pain has been treated with intermittent administration of parenteral opiate analgesics. The intravenous (IV), subcutaneous, and intramuscular (IM) delivery is the usual route of providing pain relief. Often a standard drug, dose, and routine dosing interval is ordered. Too frequently, satisfactory postoperative analgesia is not achieved with a routine approach. Today, with the wide variety of opioid-like drugs, each complete with a characteristic potency, onset, duration of action, and side effects, a practitioner can tailor individual postoperative analgesia regimens for each patient. The goal of opiate administration is to find the often narrow therapeutic window between patient agony with respiratory splinting and excessive patient sedation with respiratory depression.

HISTORY

The first physiologic research was reported in 1665 by Christopher Wren, an English architect.[8] He injected crude opium into a

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cutdown venous access in the hind paw of a dog and noted the hypnotic effect. Morphine was first extracted from crude opium in the early 1800s. Fredrich Meisner is reported to have named the alkaloid "morphine" in 1803.[27]

Historians disagree on the correct gender of the namesake of the first opiate analgetic, named after either Morphina the Greek goddess of sleep or Morpheus the Greek god of dreams. By the middle of the 19th century the use of the isolated alkaloid rather than crude opium gained popularity. In the 1840s, England imported crude opium, also called gum opium, intended for medical use, from the island of Hong Kong.[27] In the 1850s, the invention of the syringe and hollow needle (Rynd, 1845, Wood, 1854) allowed physicians to administer measured amounts of morphine accurately for the first time.[8]

Hydromorphone was introduced in 1926, followed by meperidine in 1938. Post-anesthesia rooms were well established by the late 1940s in an effort to provide monitored care in the immediate postsurgical period. In those early recovery rooms, pain was recognized as a postoperative problem, yet generally undertreated. The ability to assist or control ventilation in a recovery room setting was not available, hence greatly increasing the risk of respiratory depression from morphine. At this time morphine and the few other semisynthetic narcotics were administered in very small doses, delivered IM or subcutaneously. IV access for intraoperative and postoperative fluid and medication administration was not routine.[6]

Today there are many synthetic opiates, most developed and distributed by the Janssen Laboratories. The future promises new drugs, new equipment, and new physiologic research that may be adapted and utilized to provide better and safer postoperative analgesia.

PAIN AS A POSTOPERATIVE PROBLEM

The state of pain following a surgical procedure is the combination of pain as a specific sensation due to a nociceptive response to tissue damage and pain as suffering. Postoperative pain includes both the original sensation and the reaction of the patient to that sensation.[31] Systemic opiates modulate the response to pain by acting at several sites in the CNS. The result of adequate opiate analgesia is a significant increase in the patient's tolerance of the painful stimulus. The patient may admit to the pain sensation, yet state that the pain is not bothersome.[9]

Uncontrolled pain in the postoperative period can have detrimental physiologic effects. It can slow the patient's recovery from surgery. It can contribute to postsurgical morbidity.[29] Depending on the operative site, pain can greatly impede return of normal pulmonary function. Splinting, inability to cough, and bronchospasm can promote atelectasis and postoperative pulmonary complications. In addition to its pulmonary effects, pain can promote immobility and hence contribute to the development of significant thromboembolic events. Severe pain can cause nausea and vomiting and further postoperative ileus. A pain-induced accelerated catecholamine response can increase systemic vascular resistance, increase cardiac work, and myocardial oxygen consumption.[29] Patient irritability and agitation may advance the likelihood of inadvertent extubation, disconnection of arterial and intravenous lines, and disruption of continuous postoperative monitoring. Clearly, halting the surgical stress response should continue into the postoperative period.

Parenteral opiates are usually required to provide adequate analgesia for postoperative and post-traumatic pain. Sriwatanakul et al[30] studied patterns of postoperative pain management by reviewing 526 charts, interviewing 81 of these patients and evaluating returned questionnaires from house and nursing staff at a large teaching hospital. The study concluded that most pain can be effectively relieved by choosing the right drug, and proper dose and dosing interval.

The investigators believed that patients and nurses were responsible for undertreating because significantly less than the ordered amount of pain medication was administered. In addition, physicians often prescribed drugs and dosing regimens that were incompatible with the accepted pharmacologic profile of the drug. It was speculated that tradition plays an important role in modeling the postoperative pain medication ordering habit of house staff. The study concluded that comprehensive education of patients, nurses, and physicians may enable the development of more satisfactory postoperative analgesia for each individual patient.

Guidelines for drug selection, dose selection, dosing frequency, and route of administration must be flexible. Designing a pain management plan in the postoperative period often requires daily evaluation of the patient's physiologic course, psychologic status, and surgical recovery progress. It is a management regimen of calculating daily total doses, assessing patient response, nursing care needs, contemplating medication options, and then prescribing the optimal analgesia plan.

It must also be recognized that in some postoperative patients, despite the most optimal parenteral opioid analgesia regimen, therapeutic pain relief will not be achieved. The patient who undergoes upper abdominal surgery, a thoracotomy incision, or sustains extensive chest wall injury may not achieve adequate comfort, respiratory ease, and ambulation with only systemic opiate analgesia. The "gold standard" treatment modality for these patients may be intraspinal opioid agonist drug administration, nerve blocks, PCA utilization, cryoanalgesia, pleural catheter techniques, or a combination of these therapeutic interventions.

CURRENTLY AVAILABLE OPIOID PREPARATIONS FOR POSTOPERATIVE ANALGESIA

The drugs acting at the opioid receptors are divided into agonists, partial agonists, agonist-antagonists, and antagonists (Table 1). Ago-

Table 1. *Currently Available Opioid Preparations for Postoperative Analgesia*

OPIOID AGONISTS	OPIOID PARTIAL AGONISTS	OPIOID AGONIST-ANTAGONIST
Morphine	Codeine	Pentazocine
Hydromorphone	Propoxyphene	Nalbuphine
Oxymorphone	Buprenorphine	Butorphanol
Meperidine		Dezocine
Methadone		Bremazocine
Fentanyl		
Sufentanil		
Alfentanil		

nists are drugs capable of eliciting a maximum possible response, such as fentanyl, morphine, and methadone. Drugs with less intrinsic activity with a less than maximum response are termed partial agonists. They also tend to exhibit a ceiling effect or a plateau level of response beyond which further dosing delivers no further pain relief. The mixed agonist-antagonists show subsequent reduction in analgesic activity with progressive dosing beyond their plateau level.[4] Included in this group are pentazocine, nalbuphine, and butorphanol. The opioid antagonist naloxone competitively blocks agonist activity at the receptor.

PHYSICAL DEPENDENCE TO OPIATES

Physical and psychological dependence is rarely a problem in postoperative patients if the narcotics are discontinued within a 3-week period. In general, when postoperative pain is being treated and the opioid drug dose is tapered accordingly, physical dependence does not develop.[3] When opiate administration is excessive and extends beyond the expected postoperative period, concern for the development of dependence is warranted. In the postoperative patient with previous habitual narcotic use, the above axioms do not exist. Optimal opiate analgetic selection, dose, and dosing interval is often difficult to attain. The patient may require what seems to be excessive postoperative opiate analgesics. Drug-seeking behavior can be perplexing to distinguish from the agony of postoperative nociceptive input from incisional tissue damage.

OPIATE SIDE EFFECTS

Opioid-like drugs act upon stereospecific and saturable receptors in the CNS and other tissues.[5] The activation of this opiate receptor modulating system in turn activates other neurotransmitter systems.

Table 2. *Analgesic Equivalents to Morphine, 10 mg IM*

	INTRAMUSCULAR (MG)	ORAL (MG)
Opioid agonists		
Codeine	130	200
Heroin	3.0–5.0	
Hydromorphone	1.5	6.0–8.0
Meperidine	75	400
Methadone	8	10
Morphine		30–60
Oxycodone	15	30
Opioid agonist-antagonists		
Buprenorphine	0.3–0.4	
Butorphanol	2.0	
Nalbuphine	10	
Pentazocine	50	

The system is complex, especially with the isolation of receptor subclasses and identification of their selective physiologic action. With receptor agonist activation comes analgesia and other side effects. The postoperative analgesic window often overlaps with the incidence of side effects. It is difficult to deliver complete analgesia without some degree of undesired effects such as excessive sedation, nausea, decreased gastrointestinal transit, and others.

The side effects for morphine are characteristic of other opiate drugs. Noteworthy differences may effect the tailoring of specific narcotic management in the individual postoperative patient (Tables 2 and 3).

Respiratory Depression

Maximum respiratory depression occurs within approximately 7 minutes after IV administration of morphine. It may be delayed for

Table 3. *Opiate Duration of Analgesic Action in Hours*

	HOURS
Opioid agonists	
Codeine	3
Hydromorphone	2–3
Meperidine	3–4
Normeperidine	14–21
Methadone	3–4
Morphine	2–3
Opioid agonist-antagonists	
Buprenorphine	3–6
Butorphanol	2.5–3.5
Nalbuphine	5
Pentazocine	2–3

as long as 30 minutes after IM administration or as long as 90 minutes following subcutaneous administration.[13]

The primary mechanism of opioid-induced respiratory depression is a decreased response of the brain stem ventilatory control center to increasing carbon dioxide tension. A 20 per cent increase in arterial carbon dioxide tension can be expected in patients with adequate opiate analgesia.[33] Respiratory minute volumes may be reduced for as long as 4 to 5 hours with a single therapeutic dose of morphine. With an equianalgesic dose of methadone, respiratory depressant effects can be detected for more than 24 hours.[25] Natural sleep can also produce a decreased ventilatory response to Co_2 accumulation. This sleep effect is additive to the respiratory depressive effect of morphine analgesia.[13]

Morphine also depresses the cough reflex. The effective plasma concentration to suppress the cough is significantly lower than the therapeutic analgesia plasma level. Inhibition of the cough reflex may delay airway secretion clearance and may contribute to postoperative atelectasis.

Nausea and Vomiting

Opioids can stimulate the chemoreceptor trigger zone (CTZ) of the medulla, producing nausea and vomiting. This emetic effect is relatively uncommon in the recumbent patient given therapeutic doses of morphine. In contrast, nausea occurs in approximately 40 per cent, and vomiting, in 15 per cent of ambulatory patients given 15 mg of morphine subcutaneously, suggesting a vestibular component to opiate-induced emesis.[13] Drugs that are useful in reducing motion sickness, such as transdermal scopolamine, are sometimes helpful in reducing nausea and vomiting in postoperative patients.

Constipation

Intestinal transit is delayed with therapeutic opiate analgesia. Small intestinal propulsive contractions are markedly decreased even though segmental smooth muscle tone rises. In the large intestine, the smooth muscle tone is also increased, to the point of spasm, yet peristaltic waves in the colon are reduced. As a result of delayed transit, additional absorption of water occurs. The combination of diminished forward motility, augmented dessication of the feces, and raised anal sphincter tone results in constipation.

Sphincter of Oddi Spasm

The enhanced smooth muscle tone also increases biliary tract pressure, which is associated with biliary colic, presenting as epigastric or chest pain. The smooth muscle spasm preventing gallbladder emptying is reversible by the administration of naloxone[22] or glucagon, 2 mg.[17]

Studies summarized by Stoelting[32] clarify the degree of intrabiliary pressure changes induced by four common opioids. Equal analgesic doses of fentanyl, morphine, meperidine, and pentazocine increase common bile duct pressure 99 per cent, 53 per cent, 61 per cent, and 15 per cent above predrug levels, respectively. Though changes in biliary tract pressure occur, the incidence of spasm of the sphincter of Oddi is about 3 per cent in patients receiving an inhaled anesthetic supplemented with fentanyl.[17]

Hypotension

IV administration of morphine does induce the release of histamine. With therapeutic analgesia provided by systemic morphine, peripheral arteriolar and venous dilatation can be seen. Marmens et al evaluated the release of histamine by equianalgesic doses of three opioids.[21] They found that the drug-induced histamine release of morphine is not characteristic of high plasma concentrations of fentanyl or oxymorphone. If the patient receiving therapeutic doses of morphine is normovolemic and supine, minimal to no changes in blood pressure or cardiac output occur. If the patient sits up or ambulates, orthostatic hypotension may occur and manifest as symptoms of nausea and fainting.

ROUTES OF OPIATE ANALGESIA ADMINISTRATION

Intravenous

IV administration of analgesics has the primary advantage of a rapid onset of pain relief. In addition, IV administration delivers a more predictable maximum concentration by eliminating the absorption process characteristic of oral and IM administration.

The two major disadvantages reduces the efficacy of IV bolus injections for postoperative pain management. (1) The analgesic effect is relatively short as plasma levels rapidly decline as distribution and elimination occur. (2) A large dose may be required in order to deliver analgesia for a longer time. This initial dose may result in toxic plasma concentration for a period of time.[16]

Constant IV infusions have found more frequent utilization in surgical intensive care units (ICU).[24] The close patient observation in an ICU allows early detection of accumulating plasma concentrations that are in the toxic range. IV narcotic infusions coupled with demand bolus analgesia have become an available delivery mode in many new PCA devices.

Using another opioid, Gourley et al illustrated that IV methadone may be superior to IV morphine as the duration of pain relief from a postoperative dose is longer. The investigators titrated IV methadone to minimum effective concentration in patients undergoing upper abdominal surgery and found a mean duration of satisfactory postoperative analgesia of 22 hours.[13] In contrast, with a single dose of intravenous methadone, the mean duration of analgesia is 3 to 4 hours.

Subcutaneous

Following the development of the syringe and hollow needle, subcutaneous administration of morphine became the earliest route of administration. The morphine base was melted down into a liquid, drawn up into a syringe, and injected via a hollow needle into subcutaneous tissue.[6] Injection site tissue irritation from large volumes of subcutaneous infusions prevented the wide utilization of this delivery route.

The subcutaneous route is now used primarily for expected long-term analgesic administration. Cancer patients are the main beneficiaries of this narcotic route today. Highly concentrated narcotics are delivered in small volumes to prevent injection site tissue damage. The site should be changed every 5 to 7 days. The site of choice for delivery is into a subcutaneous part of body that will not interrupt free motion, like on the chest wall.

Intramuscular

Probably the first widespread use of IM morphine was in World War II. Prepackaged and single-dose syringes of morphine called syrettes were used to combat post-traumatic pain. Administered in the field by medics or aidmen, the final deposition of morphine in either the IM or subcutaneous site yielded unpredictable absorption. Inadequate post-injury pain relief or respiratory depression from repeated doses was not infrequent.[6]

Austin et al studied postoperative patients receiving IM meperidine, 100 mg, at fixed 4-hour intervals. They found wide variations in systemic levels with minimum effective concentrations achieved only 35 per cent of each dosing interval. They believed that absorption from the IM injection was the cause of such variability in concentration, time to peak concentration, and resultant analgesic effects.[1]

Drug selection may contribute to the quality of postoperative analgesia delivered IM. Pain relief quality and duration of analgesia was superior in postsurgical patients receiving IM buprenorphine (0.3 to 0.6 mg) compared with morphine (10 to 20 mg) in equianalgesic doses.[26] Both drugs have similar mean durations of analgesic action, with the severe pain returning to baseline pain in 3 hours. However, the patients receiving buprenorphine injections had a broader standard deviation of mean duration of pain relief, with more patients experiencing analgesia for longer than 6 hours.

Transdermal

Fentanyl is the first opioid-like drug to receive extensive trials in a transdermal delivery system. Caplan et al studied 14 patients undergoing shoulder surgery with regional anesthesia.[7] Each received either transdermal fentanyl, designed to deliver 75 μg per hour, or inactive placebo placed on the nonoperative side of the upper chest wall. Results showed a significant improvement in postoperative analgesia in the transdermal fentanyl group and expressed lower pain visual analogue scores. The experimental group required less IM morphine for the first 24 hours. The increased pain relief was coupled with increased rates of vomiting in the study group versus the placebo transdermal patch group.

Oral (Sustained Release)

The oral sustained-release system is usually made of cellulose polymers. Release occurs when the drug-polymer mixture is exposed to the gastrointestinal fluid, resulting in hydration of the drug matrix and release of drug from the tablet.

Fell et al[11] studied postoperative pain management in patients undergoing hysterectomy or cholecystectomy. He concluded that sustained-release morphine can be a convenient, safe, and effective mode of postoperative analgesia. In contrast, Banning et al studied a similar group of surgical patients by administering sustained-release morphine both preoperatively and postoperatively. She found that the controlled release morphine failed to provide satisfactory analgesia, as seven of the ten patients in the study group required rescue analgesics within 6 hours of initiation of the study.[2]

Sustained-release morphine may not be suitable for postoperative pain management for several reasons. The Banning study concluded that controlled-release morphine often does not provide satisfactory postoperative analgesia. In addition, gastric emptying may be delayed during surgery resulting in an accumulation of enteral morphine. This may expose the patient to delayed absorption, producing a toxic systemic level. Oral controlled-release morphine may be best suited to providing analgesia for cancer pain.

Sublingual

Sublingual administration of opiates is a new and convenient method of postoperative medication. Sublingual dosing delivers the drug into the systemic compartment, avoiding the first pass extraction by the liver.

Buprenorphine (mu partial agonist) has become the prominent opioid-like drug for sublingual delivery owing to its high lipophilicity and hence its high bioavailability.[10] The transfer of an opiate through the buccal and sublingual mucosa is dependent on the lipid partition coefficient. The drug is void of bad taste and mucosal irritability. Sublingual buprenorphine appears to be an appropriate alternative to morphine injection in children after orthopedic surgery.[22, 28]

The role of sublingual administration of a narcotic may find a place as a premedication.[28] With the added benefits of no injection discomfort and incurring less side effects of nausea, vomiting, and respiratory depression, it may also be helpful in contributing to intraoperative anesthesia, postoperative analgesia, and for cancer pain.

Intranasal

Butorphanol, delivered intranasally in metered doses, is reported to be effective for the relief of moderate to severe postoperative pain.[19] Intranasal butorphanol has also been used as a preoperative medication, to supplement balanced anesthesia, and to relieve prepartum pain and post-dental surgery pain. Butorphanol has minimal risk for respiratory depression and is not a controlled substance.

Rectal Absorption

Drugs exposed to the rectal mucosa are taken up into the submucosal venous plexus. The preparation matrix is a hydrophilic polymer gel. The morphine is taken up and held in the matrix and then dried. The drug is released on rehydration. Part of the narcotic drains into the portal system via the superior rectal vein. The rest of the drug drains into the systemic circulation via the middle and inferior rectal veins. This portion of the drug then drains into the internal iliac veins and into the inferior vena cava, hence missing the first-pass hepatic circulation and elimination.[15]

Missing the first-pass hepatic metabolism is one major advantage to rectal administration of narcotics. In addition, this delivery mode is not dependent on gastric emptying as are medications given by mouth. Rectally administered morphine has approximately 30 per cent bioavailability, twice that of the oral route.[34] This delivery mode is also suitable for sustained-release preparation of opioids.

SUMMARY

There are many considerations when ordering postoperative analgesia. The goal of providing patient comfort, avoiding unwanted side effects, and improving recovery outcome is often difficult to attain. The choice of postoperative pain management depends on the site of surgery, patient preference, monitoring convenience, technique, and equipment availability in addition to the expertise of the patient's physicians. Today, with the wide variety of drugs and available delivery routes, the ability to provide satisfactory parenteral postoperative opiate analgesia is improving. Evaluation and evolution of each postoperative pain management regimen should occur daily. Knowledge of available therapeutics and flexibility in fulfilling these plans should ensure safe and effective postoperative analgesia for each patient.

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Patient-Controlled Analgesia: An Update on Its Use in the Treatment of Postoperative Pain

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Despite recent advances in surgery and anesthesia, many patients continue to experience unacceptable pain during the early postoperative period. Why do patients continue to suffer from acute pain when effective opiate analgesics are available? The primary reasons may relate to a lack of information about analgesic drugs and misconceptions about their potency, duration of action, side effects, and addictive potential. Many patients are prescribed dosages of analgesics that are less than half of what is actually needed to relieve their pain. In addition, nurses further reduce these dosages.

In no other area of medicine has such an extravagant concern for side effects so drastically limited treatment. Both pharmacokinetic and pharmacodynamic variability contribute to the difficulty in predicting the analgesic requirement for a given patient. Obviously, individualization of analgesic therapy is crucial if one hopes to improve postoperative pain relief. Patient-controlled analgesia (PCA) is a system that is designed to accommodate the wide range of analgesic requirements that can be anticipated when managing acute postoperative pain.

HISTORICAL PERSPECTIVE

In 1968, Sechzer described the postoperative analgesic response to small intravenous (IV) doses of opioid analgesics given on patient demand by a nurse-observer.[35] It was concluded that this "demand analgesia" system provided improved pain relief with smaller total drug dosages than conventional intramuscular (IM) therapy. Sechzer also reported that the postoperative analgesic requirement was cyclical and varied considerably among patients; however, it was consis-

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tent within each subject. Nevertheless, repeated administration of small IV bolus doses of opiate compounds was impractical because of the demands it placed on the nursing personnel.

In the late 1960s, analgesic researchers began testing instruments that would allow patients to self-administer small IV doses of opioid drugs when they felt the need.[21, 30, 36] The early PCA devices consisted of an electronically controlled infusion pump connected to a timing device. When the patient experienced pain, he triggered the device by depressing a thumb button located on the end of a cord extending from the machine. The machine then delivered a preset amount of analgesic drug into the patient's indwelling IV catheter. The timer was programmed to preclude administration of additional (supplemental) doses until a specific time period had elapsed (the so-called lockout or delay interval). The purpose of the lockout interval was to prevent the patient from administering a second dose until after the first dose had time to exert its maximal (peak) pharmacologic effect.

Increased concern about inadequacies in the conventional approaches to managing acute postoperative pain has led to renewed interest in the concept of PCA.[50,51] With this "on demand" system for managing postoperative pain, the patient is allowed to self-administer narcotic analgesic medication using a programmable infusion pump, thereby minimizing the effects of pharmacokinetic and pharmacodynamic variability on the response to analgesic medication. Recent advances in infusion pump technology now make it possible to safely administer small IV bolus doses of an analgesic using a variety of commercially available PCA devices.

CLINICAL EXPERIENCE

In 1970, Forrest and colleagues[21] described an instrument (Demand Dropmaster, Stanford, CA) that automatically administered IV analgesic drugs when activated by pressing a button on a hand grip. In a pilot study involving 30 patients, the investigators reported that both patient and physician acceptance was good and that the fail-safe features were reliable. In 1971, Sechzer[36] described his initial experience with an analgesic-demand device. It was concluded that their patient-controlled demand system was a highly satisfactory method for treating postoperative pain and that good analgesia could be achieved with relatively low total drug dosages.

Using a demand analgesia device (Demanalg, London, Ontario, Canada), Keeri-Szanto reported that the use of demand analgesia (versus conventional IM therapy) decreased the incidence of "substantial" postoperative pain from 20 to 40 per cent to less than 5 per cent.[30, 31] When the demand analgesia group returned to IM therapy, the incidence of incomplete analgesia increased to 30 per cent even though many of these patients received a larger amount of analgesic medication. More recently, these investigators have reported that demand analgesia improved early mobilization, cooperation with physiotherapy, and was associated with a 22 per cent decrease in the duration of the postoperative hospital stay (versus conventional IM therapy).[20]

Investigators at the Welsh National School of Medicine developed the first commercially available PCA device, the Cardiff Palliator (Graseby Dynamics Ltd, Watford, England).[18] In subsequent studies,[2, 9, 25, 39] they have successfully compared a wide range of analgesic medications for postoperative pain relief using their PCA device. However, Sprigge and Otton reported that some of their patients found the Cardiff Palliator's demand button hard to operate, and these investigators felt "the technique was too expensive and too time consuming."[40]

Hull and his colleagues in the United Kingdom developed a highly sophisticated on-demand analgesia computer (ODAC, Janssen Scientific Instruments, Beerse, Belgium).[28, 29] Dosage was limited by a decrease in the patient's respiratory rate and by a series of electronic fail-safe circuits. Using this device, other United Kingdom investigators reported that the postoperative pain relief provided by the "on-demand" computer was comparable to that produced by epidural bupivacaine.[52] Using an infusion of alfentanil supplemented with bolus injections on demand,[47] Welchew and Hosking recently reported that alfentanil was associated with significantly less sedation during the early postoperative period than meperidine. Lehmann and his coworkers in West Germany found that the analgesia provided by the ODAC-PCA device was judged to be superior by 36 to 47 per cent of patients when compared with their previous experiences with "conventional" postoperative analgesia.[32]

Tamsen and his colleagues in Sweden performed a series of elegant pharmacokinetic-dynamic studies using a programmable drug injector (Prominject, Pharmacia, Stockholm).[14, 41–44] These investigators reported that neither age, sex, body weight, nor the rate of drug elimination appeared to be related to the resulting therapeutic (analgesic) concentrations. Both the analgesic requirement and the resultant therapeutic concentrations were highly variable (four- to sixfold). Although individual drug concentration curves varied, patients maintained relatively constant plasma concentrations when allowed to self-administer meperidine and morphine during the early postoperative period. These investigators reported mean postoperative analgesic requirements of 2.7 ± 1.1 mg per hour and 26 ± 10 mg per hour for morphine and meperidine, respectively.[41] The most frequent complaints were drowsiness and dry mouth; however, acute respiratory depression was reported in two hypovolemic patients. Interestingly, Tamsen et al[44] have reported an inverse relationship between CSF endorphin (fraction I) concentrations and the calculated CSF meperidine levels when patients were allowed to achieve satisfactory analgesia using their patient-controlled system. These results suggest a role for the endorphins in the modulation of acute postoperative pain. For example, the presence of high levels of endogenous morphine-like substances in the brain would be expected to minimize the requirement for exogenously administered opioid analgesics during the postoperative period.

Bennett and colleagues evaluated the effectiveness of PCA using the Demanalg device for the management of postoperative pain.[1, 3–7, 23] They reported that patients maintained "a state of adequate analgesia with minimal sedation throughout their therapeutic course."[5, 7] In a study involving morbidly obese patients undergoing gastric bypass surgery, the average PCA morphine requirement was 1.7 mg per hour (with a tenfold variation).[6] Obese patients receiving PCA therapy were reported to have improved postoperative pulmonary function.[3] Compared with a matched group of patients receiving conventional IM therapy, these investigators reported that significantly less medication was required during the postoperative period in the PCA-treated group.[4] Subjective evaluation of patients following operations involving a flank incision revealed significantly less pain, less sedation, and greater activity in those subjects randomized to PCA therapy.[29] These investigators have also provided evidence for a circadian (cyclical) variation in the postoperative analgesic requirement.[23] Maximal drug usage occurred in the morning (9:00 AM), and it was minimal during sleep (3:00 AM). These investigators also report less postoperative pain, greater spontaneous physical activity, and fewer nocturnal sleep disturbances with patient-controlled (versus IM) analgesic therapy.

Unfortunately, many of the PCA studies that have been published in the surgery and anesthesia literature have been poorly controlled clinical reports utilizing subjective end points for assessing the patient's response to PCA therapy. With attentive nursing care, conventional IM therapy can become "on demand" and may be as effective as PCA.[17, 48] Using a double-blind protocol design for comparing PCA with on-demand IM therapy for postoperative pain relief, Welchew reported that the mean pain scores in the two groups were virtually identical.[17] In addition, sedation scores and postoperative pulmonary function tests were not significantly different for the two groups. Although this study has been criticized (for example, different analgesics were used for the two groups), it emphasized the necessity for carefully controlled studies comparing PCA with conventional IM therapy as well as with other newer approaches to pain management (for example, epidural narcotics, opiate infusions, transcutaneous opiates, and transcutaneous electrical nerve stimulation).

In a recently published controlled trial, Dahl and colleagues reported that when conventional PCA was compared with a "regular" IM dosage regimen (given every 4 hours) that was supplemented with IV medication on demand,[13] there were no significant differences between the two analgesia regimens with respect to pain scores, morphine dosage requirements, or side effects. Interestingly, these investigators stated that the need for supplemental IV doses in the control (IM) group to ensure optimal treatment is "hardly practicable on a normal ward." They further suggested that with the standard regular-interval regimen, "a large number of patients were either overdosed or underdosed."

More recently, two investigative groups in the United States have compared PCA with conventional IM or epidural opiates for pain control after elective cesarean section.[16, 27] Although patients in both the PCA and epidural morphine groups preferred their therapy over the IM regimen administered after their first cesarean section, only those patients receiving epidural morphine reported significantly better pain relief than those in the IM group. In addition, the PCA dosage requirement was similar to the IM treatment group. Patients' perception of sedation and activity scores did not significantly differ among the three treatment groups. However, epidural morphine produced the highest incidence of pruritis (40 to 45 per cent of the epidural-treated patients required antipruritic therapy), and this group frequently required systemic opioid supplementation during the first postoperative day.

Recent publications have described several alternative approaches for using on-demand analgesia in the management of acute postoperative pain (for example, epidural PCA,[10] sublingual PCA,[37] subcutaneous PCA[45]). In a study comparing morphine and meperidine for epidural PCA,[38] Sjöström et al reported excellent analgesia with average dosages of 0.5 mg per hour and 18 mg per hour, respectively. The epidural PCA morphine requirement was 80 per cent less than in the IV PCA group. Similar to previous studies involving IM or IV PCA, large interpatient variability existed with the epidural PCA route of administration. Subcutaneous (SQ) PCA has been reported to be as effective as IV PCA without requiring continuous IV access.[45] However, the opioid dose requirements appear to be 20 to 30 per cent higher with the SQ route of administration. Before PCA will be widely accepted in clinical practice, however, comparative studies are needed to assess the cost-effectiveness of PCA compared with other currently available therapeutic modalities for controlling acute pain.

PCA INFUSION DEVICES

The Abbott Life Care PCA Infusers (Abbott Laboratories, North Chicago, IL) combine microprocessor and stepping motor technology for the safe delivery of either intermittent bolus dose or a continuous infusion of narcotic analgesics from disposal cartridges. These relatively lightweight, portable, computerized volumetric infusion pumps have lockable security doors that prohibit unauthorized access to the analgesic drug or the controls while the unit is in operation. A liquid crystal display indicates the operational status, total cumulative dose, number of bolus doses administered, as well as other status and alarm messages. Prefilled (for example, morphine 1 mg per ml, meperidine 10 mg) or empty drug cartridges are available. After the cartridge has been inserted into the pump and the special "Y" tubing (containing a one-way check valve) has been primed, the device can be connected to an existing IV catheter.

With the first generation Life Care PCA device, the incremental (bolus) dose volume and lockout were set using thumbwheel switches. The newer (Life Care PCA plus) infuser is fully computerized and can be programmed to deliver either intermittent bolus doses, continuous infusions, or a continuous infusion, which is supplemented by bolus injections on demand. When the door is closed and the key removed, the display reads "ready," indicating that the patient can activate the device by pressing the patient-control button. Immediately after a bolus dose is delivered, the device enters the mandatory "lockout" mode for a minimum of 5 minutes. The newer version has a memory that records the administered dose as well as key events (for example, changes in the dosage regimen). While in operation, the PCA infusion pump is secured to an IV pole with a Duolock locking mechanism.

The Bard Harvard PCA (Bard Med Systems Division, Murray Hill, NJ) is a portable syringe infusion pump capable of both continuous and intermittent drug administration. In addition, this device can also be programmed to deliver a continuous background (basal) infusion, which is supplemented with bolus doses on demand. The pump has a stepper motor and is microprocessor controlled to prevent faulty operation due to an empty drug syringe, low flow, runaway, excess pressure, low battery, or control circuit failure. The alphanumeric message panel guides the operator through the sequences necessary for correct pump operation. When the pump is in the operational mode, prescription and dosage data can be read or changed only after an authorized user enters a preassigned access code. A keyswitch allows the operator to unlock the cover over the syringe compartment. A 60-ml disposable plastic syringe can be filled with the desired concentration of the prescribed opiate analgesic. The syringe is connected to a Harvard "Y" type extension set (containing a one-way antireflux valve), then it is placed in the syringe cradle and purged. The device's microprocessor-controlled memory records the total number of patient attempts during the lockout period as well as the number of successful injections to allow the operator to optimize the analgesic regimen. The memory also records key events (for example, changes in the infusion rate).

Recently, Bard has introduced a small Ambulatory PCA device. This portable device is fully computerized and battery powered (9 V). It has essentially all the features available on the original Harvard PCA device (for example, intermittent, continuous infusion or continuous [basal] supplemented on demand). In addition, it has a large drug volume capacity (either 100- or 250-ml disposable plastic containers). This PCA device also has all the fail-safe features of the larger infuser and the drug compartment is tamperproof. Special microbore tubing is available for use of the device with epidural or subcutaneous administration techniques.

The Becton-Dickinson PCA Infusor is a portable, battery-operated device. Although it is a fully computerized pump, it has simplified programming features on its liquid crystal display. The alphanumeric message panel guides the operator step-by-step through the programming procedure. The prescribed drug can be delivered from a wide variety of standard 20- to 60-ml disposable plastic syringes and the drug compartment is covered by a clear tamperproof plastic cover. This cover is locked with a key that also electronically locks the keyboard. The standard microbore tubing with an antireflex valve is available for IV use. Analogous to the other computerized PCA devices, this device has a memory (which remains operational even after the device is turned off), acoustic and diagnostic alarm features, and can be secured to an IV pole.

The Pharmacia Cadd-Pac is a small (15 oz), portable, programmable analgesic infusion device that can provide for the safe delivery of parenteral analgesics both in the hospital as well as outside the hospital environment. Although this PCA device has not been extensively evaluated for the treatment of acute postoperative pain, its compact size may allow for increased patient activity and mobility during the early postoperative period. The device delivers the analgesic drug on demand, with incremental doses ranging from 0.1 to 99.5 mg and a lockout interval from 5 to 199 minutes. The pump can also be used to continuously infuse analgesics, with a basal infusion rate of 0.1 to 99.5 mg per hour (depending on the concentration of the solution). Analgesic medication is contained in prefilled, sterilized disposable cassettes that are maintained in a locked compartment. Alarms warn the user when there is a low residual drug volume, low battery power, or a mechanical failure.

The Baxter PCA Infusor is a small nonelectronic device that is fully disposable. It consists of a lightweight plastic cylinder containing the analgesic medication inside an elastic balloon. The drug chamber holds a volume of 40 ml and the amount of drug delivered per injection is dependent on the opioid concentration. The device is nonprogrammable, delivering a fixed 0.5-ml dose at intervals of 6 minutes or longer. As the balloon reservoir slowly deflates, solution flows through a small orifice (flow restrictor), which determines the time required to fill the injection reservoir (6 minutes). The injection reservoir is located on a wristband that is activated by pushing a button. There is no drug infusion between depressions of the medication-demand button. Although its simplified design obviates the need for fail-safe features, it is less flexible than the other systems with respect to the size of the administered dose.

The On Demand Analgesia Computer (ODAC, Janssen Scientific Instruments) is a highly innovative experimental PCA device. This infusion device allows the patient to interact directly with the machine using a tape cassette.[29, 40] In addition to demand doses, this device can administer a background infusion based on the amount of analgesic drug that the patient demanded during the previous 16-minute interval. An integral pneumograph sensor prevents analgesic administration if the respiratory rate is depressed. With further technological refinement, the ODAC could become a clinically useful device in the management of postoperative pain. However, it would seem unlikely that any of the pharmacokinetically based, computer-controlled infusion systems currently under investigation will be commercially available in the near future.

MANAGEMENT OF POSTOPERATIVE PAIN

If postoperative PCA therapy is to be successful, it is important that the patient as well as the physician and nursing staff understand the basic concept.[50] As part of their preoperative instructions, the author recommends that patients (1) be given an explanation of the PCA device; (2) be told not to expect complete pain relief, but rather to use the device to avoid distressing pain; (3) be encouraged to use the device in a prophylactic manner to avoid the discomfort associated with early ambulation, physical therapy, and dressing changes; and (4) be told that an attempt would be made to minimize the size of the bolus dose during awake hours to avoid excessive sedation, while attempting to maximize the dosing interval during sleeping hours to prevent the patient from awakening repeatedly during the night.

In prescribing postoperative PCA therapy, what pharmacologic properties would be highly desirable in an opiate analgesic? The ideal drug would have a rapid onset of analgesic action, be highly efficacious in relieving pain, have an intermediate duration of action to improve controllability, not produce tolerance or dependence, and have no side-effects or adverse drug interactions. There are a large number of analgesic drugs that can be used with PCA therapy (Table 1); however, morphine and meperidine have been used the most ex-

Table 1. *Guidelines for Bolus Dosages and Lockout Intervals for Various Parenteral Analgesics When Using a PCA System*

DRUG	BOLUS DOSE (MG)	LOCKOUT INTERVAL (MINUTES)
Agonists		
Morphine	0.5–3.0	5–20
Methadone	0.5–3.0	10–20
Hydromorphone	0.1–0.6	5–15
Oxymorphone	0.1–0.6	5–15
Meperidine	5–30	5–15
Fentanyl	0.02–0.1	3–10
Sufentanil	0.002–0.015	3–10
Agonist-antagonists		
Pentazocine	5–30	5–15
Nalbuphine	1–5	5–15
Buprenorphine	0.03–0.2	10–20

From White PF: Patient-controlled analgesia: A new approach to the management of postoperative pain. Semin Anesth 4:255–266, 1985; with permission.

tensively in clinical trials. More recent studies have suggested that both hydromorphone[45] and oxymorphone[26] are excellent alternatives to morphine for postoperative analgesia.

The duration of analgesia produced by methadone and buprenorphine may be too long, while fentanyl and its newer analogues may be too short-acting when administered as incremental bolus doses. However, Gourlay et al[22] have recently described the blood concentration-analgesic response relationship when fentanyl was administered by a continuous (basal) infusion that could be supplemented by bolus injections on demand for postoperative analgesia. Sufentanil and alfentanil can also be effectively administered by continuous infusion or by a continuous plus bolus on-demand delivery mode. Sufentanil, 5- to 15-μg IV has been effectively administered for managing postoperative pain using the traditional intermittent bolus technique[12]; however, the frequency of demands is higher than with the more conventional analgesic medications. Recently, Chrubasik et al[11] reported that a continuous plus an on-demand epidural infusion of alfentanil-produced analgesia that was similar in quality to that of morphine. Because of the more rapid onset of analgesia (and lower requirement for supplemental sedative tranquilizers), these investigators felt that alfentanil was preferable to morphine. The agonist-antagonist analgesics (for example, butorphanol, nalbuphine, buprenorphine) produce ceiling or plateau effects with respect to both respiratory depression and analgesia. In those situations where agonist-antagonists can provide adequate pain relief, these drugs would be less likely to produce clinically significant respiratory depression than the pure opioid agonists.

In general, a titrated loading dose is administered to achieve adequate postoperative pain relief prior to initiating maintenance PCA therapy. The loading dose can be administered over 15 to 30 minutes in the postanesthesia care unit. When the patient is sufficiently recovered from anesthesia, they are given the patient-control button and allowed to begin self-administering small bolus doses of the analgesic medication using the PCA device. If the initial dose is inadequate (that is, pain relief consistently requires one or more bolus injections at frequent intervals), the dose is increased by 25 to 50 per cent until an effective bolus dose is determined. Conversely, if the patient experiences excessive sedation or dizziness after a bolus injection, the dose is decreased by 25 to 50 per cent. During the nighttime (sleeping) hours, the size of the bolus dose can be increased or a "background" infusion administered in order to maximize the time interval between successive doses.

The average morphine usage during the first 3 days following major operative procedures at Stanford ranged from 1.1 to 2.6 mg per hour (Fig. 1); however, there was wide variability in the individual morphine requirements.[38] In this preliminary study, 71 per cent of the patients reported no significant discomfort during the period in which they were using the PCA device. The remaining 29 per cent of the patients complained of mild-to-moderate pain at some point

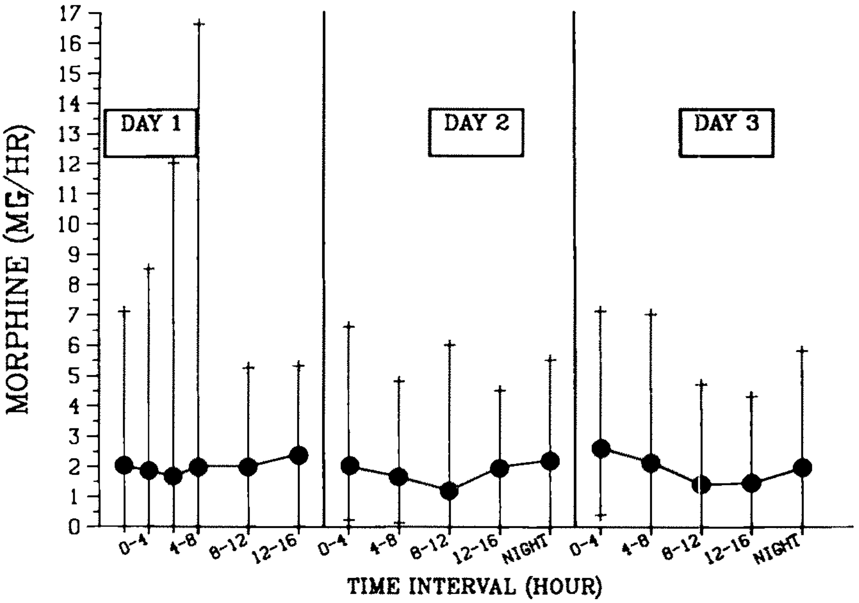

Figure 1. Postoperative morphine requirement (mg per hour) as a function of time after administration of a loading dose in the recovery room. Median hourly usage values were averaged over 4-hour intervals, with individual variability represented by the vertical bars. (*From* White PF: Patient-controlled analgesia: A new approach to the management of postoperative pain. Semin Anesth 4:255–266, 1985; with permission.)

during the study. The patients were awake and alert at least two-thirds of the daytime hours with no episodes of prolonged sedation or sleeping during the day. As expected, the level of physical activity increased with each postoperative day. In general, patients stated a preference for PCA therapy when asked to compare it with their previous experience with conventional IM injections for the treatment of postoperative pain. However, one patient preferred IM therapy because she was more sedated and therefore, had less recall of the early postoperative period.

In a comparative study at Stanford University involving PCA and conventional IM therapy, we found that PCA-treated patients required less narcotic medication to achieve comparable analgesia during the first 48 hours after orthopedic surgery (Fig. 2).[51] However, the PCA group tended to require parenteral analgesics for a longer period of time after surgery. In a similar comparison of PCA and conventional IM therapy, Bollish et al[8] reported that comparable dosages of morphine produced superior analgesia in the PCA-treated group. Although they also reported that PCA was no more effective than IM analgesics in relieving pain, Ferrante et al were able to document a complete cycle of pain every 5.3 hours in patients receiving IM opioids, but no pain cycle was seen with the use of PCA therapy.[19] A

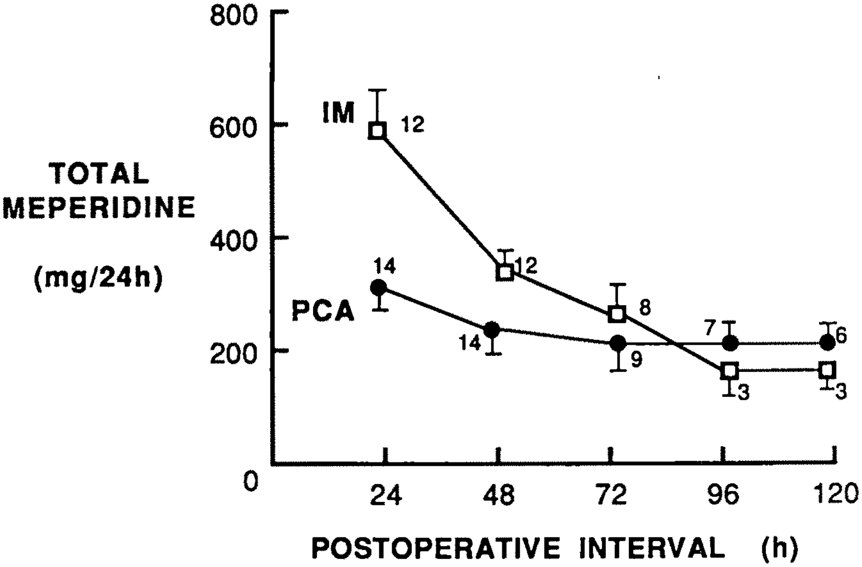

Figure 2. Postoperative meperidine dosage requirement (mg per 24 hours) for patients assigned to either IM or PCA treatment groups. The number of patients in each group receiving parenteral analgesics are indicated in parenthesis. (*From* White PF: Use of patient-controlled analgesia for management of acute pain. JAMA 259:243–247, 1988; with permission.)

preliminary study suggests that continuous infusion of opioid analgesics may be inferior to intermittent bolus administration of narcotic drugs in the relief of postoperative pain because of the more rapid development of tolerance in the infusion group.[33]

POTENTIAL COMPLICATIONS OF PCA THERAPY

The risk of clinically significant postoperative respiratory depression in a patient receiving PCA therapy is extremely low. Nevertheless, some investigators have suggested that special precautions (for example, use of pulse oximetry, apnea monitoring) should be taken to minimize the risk of this potentially life-threatening complication. Importantly, patients undergoing a variety of major operations have maintained normal arterial blood gases in the early postoperative period while receiving PCA therapy.[42, 52]

In a study involving patients undergoing upper abdominal operations, the PCA-treated group had more patients with mildly elevated capillary carbon dioxide levels than patients receiving either IM or epidural narcotics.[48] Yet, postoperative respiratory function in patients receiving PCA therapy was not significantly different from IM-treated patients.[31, 32, 48] Administration of large bolus doses of an-

Table 2. *Summary of Problems That Can Occur During Patient-Controlled Analgesia Therapy*

- Operator errors
  - Misprogramming PCA device
  - Failure to clamp or unclamp tubing
  - Improperly loading syringe or cartridge
  - Inability to respond to safety alarms
  - Misplacing PCA pump key
- Patient errors
  - Failure to understand PCA therapy
  - Misunderstanding PCA pump device
  - Intentional analgesic abuse
- Mechanical errors
  - Failure to deliver on demand
  - Defective one-way valve at "Y" connector
  - Faulty alarm system
  - Malfunctions (for example, lock)

From White PF: Mishaps with patient-controlled analgesia (PCA). Anesthesiology 66:81–83, 1987; with permission.

algesics to elderly or hypovolemic patients can produce clinically significant respiratory depression.[20] Although no respiratory arrests have been reported in the medical literature during PCA therapy, it is important to frequently assess the drug dose-effect relationship during the early postoperative period. Adjustments in the bolus dose or infusion rate on an individual basis are required in order to optimize the therapy and prevent untoward side effects. The most common problems with PCA therapy are related to operator errors (Table 2).[49] If errors are to be avoided, the nursing staff must understand the conceptual basis for the therapy as well as be knowledgeable about the operational aspects of the PCA pump.

With repeated or continuous administration of narcotic analgesics, tolerance will develop to the desirable as well as the undesirable pharmacologic effects. As a result, progressively larger narcotic doses may be required to produce the same degree of pain relief during the postoperative period. When narcotic analgesics are discontinued after a prolonged period of treatment, patients may experience withdrawal symptoms as a result of the development of physical dependence. However, addiction or psychological dependence (that is, compulsive drug-seeking behavior) rarely, if ever, develops in patients receiving narcotics for the treatment of acute postoperative pain.

SUMMARY

It is impossible to accurately predict how much pain a patient will experience after an operation or how much analgesic medication will be required to provide adequate pain relief. Thus, physicians and nurses necessarily rely on subjective methods to determine the analgesic regimen for patients experiencing postoperative pain. In reviewing the literature, it is obvious that "there is a deficient link in the chain that involves the patient who experiences pain and requests medication, the physician prescribing the analgesic drugs, and the nurse who assesses the pain and makes the decision about when to administer analgesics."[46] Problems arise because of the inherent difficulties in determining the appropriate dose and dosing interval, resulting in some patients being overmedicated while others continue to experience unacceptable levels of pain. Given the narrow "therapeutic window" for an individual patient, a carefully titrated dose of analgesic drug is needed to maintain adequate analgesia without undesirable side effects.

PCA is a system designed to accommodate the wide range of analgesic requirements that can be anticipated when managing acute postoperative pain.[33] PCA can also minimize the anxiety resulting from the slow onset of pain relief associated with most commonly used therapeutic modalities. A major psychological advantage with PCA therapy relates to its ability to minimize the time delay between the perception of pain and the administration of analgesic medication. In addition, the increased attention being paid to the PCA-treated patient both preoperatively and postoperatively might provide a psychological benefit to the patient. The comfort that patients experience as a result of compassionate and attentive nursing and medical care would be expected to significantly decrease their analgesic drug requirement.[15]

Although the concept of PCA therapy is not new,[21, 30, 36] recent progress in the area of infusion pump technology has renewed interest in this concept. Early clinical studies have demonstrated that safe and effective postoperative pain relief can be achieved with a variety of PCA infusers. With PCA therapy, Graves et al have reported that patients experience minimal sedation during awake hours and progressively increase their physical activity during the postoperative period.[24] These investigators suggested that results are better when patients control their own analgesia.

In the postoperative situation, PCA is used for *maintenance* of analgesia. Thus, patients should receive a titrated loading dose prior to initiating self-administered analgesic therapy. If the therapy is to be successful, it is important that the nurse assess the individual patient's response to the analgesic regimen. Given the marked pharmacodynamic variability that exists among patients with respect to their postoperative analgesic requirements, it will occasionally be necessary to alter the amount of the bolus dose and the duration of the lockout interval in order to optimize the therapeutic regimen. To achieve optimal results with PCA, both the patient and the staff should understand the basic principles upon which the therapy is based. Finally, applications of PCA therapy are not limited to the postsurgical ward. This concept can be applied to the management of acute and chronic cancer pain on medical and oncology wards. Others have suggested that PCA therapy could be used in obstetric suites, intensive care units, coronary care units, as well as in clinical research.

Individuals with either markedly increased or decreased analgesic requirements can be adequately managed using a PCA delivery system. Thus, the rational use of a PCA infusion device allows the individual to overcome variations in both pharmacokinetic and pharmacodynamic factors by titrating the rate of narcotic administration to meet their individual analgesic needs. If recurrent (or intractable) nausea or vomiting develops, the patient can be switched to a different narcotic analgesic or antiemetic therapy can be administered. The commonly used antiemetic drugs (for example, droperidol, hydroxyzine) would be expected to enhance the sedation produced by the opioid analgesics.

In conclusion, PCA provides improved titration of analgesic drugs, thereby minimizing individual pharmacokinetic and pharmacodynamic differences. PCA therapy decreases patient anxiety resulting from delays in receiving pain-relieving medication and from the slow onset of analgesic action when these drugs are administered either intramuscularly or in the extradural space. With PCA therapy, patients are able to maintain an acceptable level of analgesia with minimal sedation and few side effects. The potential for overdose can be minimized if small bolus doses are used with a mandatory lockout interval between successive doses. Finally, studies of the cost-effectiveness of PCA therapy are important if this therapeutic approach is to achieve even more widespread acceptance.

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Spinal Analgesia

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Postoperative analgesia by placement of medication in the spinal canal was reported as early as 1949.[22] This "new" method has experienced a marked rise in popularity since opiate receptors were located in the spinal cord[5] and spinal (epidural or intrathecal) opiates were determined to have "regional analgesia" properties.[24, 100] Academic and private hospitals throughout the world are using this technique, with varied results as reported in the literature. Offering this service should not be undertaken lightly, however. The technique (either intrathecal narcotics or epidural narcotics and local anesthetics) has a low therapeutic index and wide patient variation in response. Good patient rapport, follow-up, and 24-hour-a-day availability are needed to provide this service safely. Information in this article is designed to help make good choices for a given department and patient needs.

PHARMACOKINETICS AND PHARMACODYNAMICS

An understanding of narcotic and local anesthetic pharmacokinetics in the epidural and subarachnoid space is necessary to use the possible drugs to one's best advantage. Known factors that may affect narcotic activity are lipid solubility, pre-existing plasma levels, receptor-binding affinity, volume of injection, and molecular weight. Systemic effects may also contribute with prolonged administration or long-acting narcotics. Lipid solubility seems to be the most important factor determining onset, spread, and duration of analgesia. Bromage et al[14] described the time course and effects of rostral spread of epidural morphine, one of the lowest lipid solubility narcotics. This demonstrates the following clinical effect of spinal opiates: less lipid-soluble narcotics have slower onset, greater dermatomal spread, and longer duration than more lipid-soluble narcotics. Other effects on spinal narcotic action are minimal compared with this effect of lipid solubility, with few exceptions. Torda and Pybus[94] described the duration response in an elegant within-patient crossover study using morphine (apparent partition coefficient [APC] = 1.4), methadone (APC = 116), meperidine (APC = 39), and fentanyl (APC = 813). In this study, the only deviation from the lipid solubility axiom was that methadone lasted longer than meperidine (mean duration 8.7 and 6.6 hours, respectively). It should be noted that narcotic duration of action depends somewhat on dose, pain stimulus, and patient population; between-study comparisons are essentially invalid.

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Several studies[21, 83, 97] have demonstrated in well-controlled, double-blinded comparisons of lipophilic narcotics (fentanyl, sufentanil, and alfentanil) versus morphine, that lipophilic narcotics have significantly more rapid onset by epidural application. Although various studies with individual narcotics intrathecally show this same trend, the author is unaware of a single study investigating analgesia and comparing two or more intrathecal narcotics of differing lipophilicity.

The issue of dermatomal spread is less clear. Although all authors seem willing to ascribe this increased spread to morphine, regarding respiratory depression, with other lipophilic narcotics having "less risk," there seems to be less agreement on the importance of catheter placement or volume of injection with lipophilic narcotics. Two studies have demonstrated little to no difference in analgesia or dose using thoracic or lumbar epidural administration of morphine for pain after upper abdominal[56] or thoracic[36] surgery. This result is in accord with morphine's low-lipid solubility. These studies used high enough volumes of injection to deliver some of the morphine to the appropriate dermatomes from the lumbar catheters; low volumes or a low-volume infusion would give a more precise delineation. No such study has been done with a lipophilic narcotic. A recent abstract by Birnbach et al[9] demonstrated improved analgesia (but not necessarily greater dermatomal spread) with increased volume of diluent for epidural fentanyl in equal doses.

Three theoretical causes of high lipid solubility effects are (1) rapid diffusion through the dura (if epidural) and into the lipid-rich spinal cord; (2) rapid uptake by lipid-rich tissues in the epidural space; and (3) rapid vascular uptake from the epidural space. Gourlay et al[37] stated a good argument for dismissing the rapid vascular uptake. In their study (and in others), epidural morphine has a faster peak plasma level than epidural meperidine. However, very lipophilic narcotics like sufentanil[42] and fentanyl[48] develop rapid peak plasma levels after epidural bolus. Although epidural tissue uptake remains an undetermined quantity, this study and one by Sjostrom et al[91] demonstrated a more rapid dural penetration with meperidine as compared with morphine. Because both of these narcotics have approximately equal molecular weight (247 and 285, respectively), the contribution of molecular weight to dural penetration is in doubt. An in-vitro study[63] demonstrated a possible effect of molecular weight and molecular shape, however.

One very important feature in these studies is the wide variation in CSF levels between patients. Although methods of measurement add some variability to results, the data demonstrate large differences in peak levels and duration of drug in the CSF.

The study by Gourlay et al[37] demonstrated rapid appearance of meperidine in lower cervical CSF after lumbar epidural administration, indicating brain levels and side effects are certainly possible with this and probably other lipid-soluble narcotics. However, peak CSF levels occurred between 10 and 60 minutes (fairly rapid onset) and relatively less meperidine reached the cervical CSF when compared with morphine. This is thought to be because of increased spinal cord uptake as meperidine moves up in the CSF.

Although not tested in any literature the author has seen, preexisting plasma levels of a narcotic would theoretically decrease its absorption when epidurally or intrathecally applied, both from the epidural space and the CSF. This would result in higher levels in the CSF for a longer period of time.

High receptor-binding affinity has been postulated as the cause of relatively prolonged spinal analgesia in the lipophilic drugs sufentanil,[28] buprenorphine,[38, 55] and lofentanil.[8, 25] Further investigation is necessary to prove this relationship, particularly that the prolongation is not simply a dose-response effect. It would appear to the author that further studies with lofentanil and perhaps others will demonstrate a significant clinical effect on duration from receptor-binding affinity.

The effect of volume of injection on the pharmacokinetics of epidural narcotics is inconclusive at this time. The study by Sjostrom et al[91] demonstrated no difference in CSF morphine levels when the same dose was given in 1 or 10 ml. This is consistent with clinical studies demonstrating equal effectiveness of morphine through a lumbar or thoracic epidural for an upper abdominal incision (T7 to T12 dermatomes).[56] Sjostrom's CSF levels were drawn from lumbar catheters, not indicating whether increased levels occurred at thoracic dermatomes.

The real question relates to the more lipophilic narcotics, however. If they are rapidly taken up by the spinal cord, it may not be appropriate to apply them in low volumes into the lumbar epidural or intrathecal space for thoracic or upper abdominal postoperative pain. Although no pharmacokinetic study has determined this to my knowledge, many centers are currently using thoracic epidural catheters to use lipophilic narcotics for thoracic or abdominal pain. In the author's experience, this is very important for delivering satisfactory analgesia with doses less than those required for systemic analgesia.

Intrathecal and epidural local anesthetics have been in use longer than narcotics and the pharmacokinetics are better understood. Intrathecal local anesthetics have not been used much for postoperative pain (see Techniques section later in this article), so epidural pharmacokinetics are discussed here. As with narcotics, initial spread of local anesthetic in the epidural space by bolus (and, to a lesser extent, infusion) is determined primarily by the volume of the injection. The drug then diffuses into epidural nerve roots and through the dura and CSF to the intradural nerves and spinal cord where interruption of axonal impulse transmission is its site of action. A significant amount of the drug remains in the epidural tissue (dissolved in fat or protein bound) where it may act as a slow-release depot as drug is distributed away from the site. Clinically, a differential block occurs depending on the local anesthetic concentration. C-fibers (postganglionic autonomic and some pain transmission) are the most sensitive to blockade, followed by sensory and then motor block with increasing concentration (the information here regarding local anesthetic pharmacokinetics is condensed and somewhat oversimplified; a more extensive review is available by Tucker and Mather[26]). Bupivacaine has a propensity for sensory block with less motor block and is the most common local anesthetic used for postoperative pain.

Local anesthetics are removed by vascular uptake with little local metabolism demonstrable. Peak plasma levels of bupivacaine occur in 15 to 30 minutes, as reported by most studies,[26] with an elimination half-life of 2.5 to 3 hours. Doses required by bolus or infusion depend on the number of dermatomes to be blocked, the strength of block desired, and interpatient variations both in dermatomal spread and sensitivity to blockade. Regarding toxicity, doses required for epidural analgesia by bolus technique are sufficiently high to approach toxic CNS symptoms. These symptoms include dizziness, ringing in ears, strange (often metallic) taste, confusion, somnolence, and ultimately unconsciousness, with or without seizures. Reports of such symptoms are rare unless intravascular injection occurs. Infusions avoid intermittent peak levels, reducing risks of toxicity.

TECHNIQUES

There are several specific questions to ask regarding use of spinal analgesia in a given patient. Should intrathecal or epidural administration be used? Shall it be applied by intermittent bolus or infusion? Should local anesthetics and/or narcotics be applied, and which narcotic? The answers to these questions depend on the patient, the pain stimulus, your practice, and the hospital where you work.

Two major factors determine the use of intrathecal analgesia: risk of "spinal headache" with multiple dural punctures and risk of infection or nerve damage with intrathecal catheters. These factors limit intrathecal analgesia to single-shot administration in most practices. A long-acting analgesic is therefore most appropriate and morphine has been the drug of choice. Doses reported in the literature have been as high as 20 mg[87] but most current recommendations are for 0.5 mg or less. Onset of analgesia takes 15 to 45 minutes, so administration with local anesthetics (if spinal anesthesia is used for surgery) or perhaps a fast-acting lipophilic narcotic can deliver rapid analgesia. As other long-acting narcotics are investigated (beta endorphin,[69] lofentanil[8]), their use intrathecally may increase. Currently, there are no local anesthetics marketed that last as long as morphine intrathecally. Dose-dependent side effects (motor block, hypotension) make their use impractical intrathecally as well for postoperative analgesia.

Epidural administration allows the safe placement of a catheter for multiple or continuous dosing. Advantages of intermittent boluses are that doses are fairly easily administered without requiring elaborate pumps. This is probably the most frequent method of spinal analgesia today. It does present some drawbacks, however. Either the physician must be available for injections 24 hours a day or a system must be developed where other personnel inject the catheters. Ready et al[80] describe a system where floor nurses inject the catheter for the pain service.

Doses and dosing intervals are determined by one of two methods: predetermined calculations or when the patient complains of pain. With the first method, there is risk of relative overdosage, particularly with the wide patient variation noted previously. With the second method, time required to acquire the medication and inject it, along with time before onset, causes the patient to experience a certain amount of pain. With both methods, the patient experiences periodic peak levels significantly above those required for analgesia, with the attendant risks of dose-dependent side effects and complications.

Narcotics used by bolus technique can be lipophilic if frequent administration is feasible. This reduces the risk of *delayed* respiratory depression, a complication almost exclusively seen with morphine. Respiratory depression does occur with these agents[2] but is usually seen within 1 hour. Local anesthetics have often been used by bolus as well; this generally requires a physician to be present to manage possible intrathecal or intravascular (IV) injection, as well as hypotension from sympathetic blockade. Another consideration is the patient's cardiovascular response to intermittent sympathetic block; periodic major fluctuations in peripheral resistance and effective volume, with or without sympathetic cardioaccelerator block, can be disastrous in patients prone to myocardial ischemia or congestive heart failure.

Tachyphylaxis with intermittent local anesthetic epidural injection is a well-documented phenomenon,[10] particularly with shorter-acting local anesthetics. Boluses must be more frequent and of higher concentration over time to achieve the same effect. Bupivacaine (a long-acting local anesthetic with predilection for sensory block[11]) has been predominantly used to minimize tachyphylaxis. As dose requirements increase, so does the risk of systemic toxicity from peak levels of subsequent injections.

Continuous infusions of epidural narcotics or local anesthetics decrease several of the previously listed risks and problems. It should be noted at this point that the literature is very confusing regarding the term *continuous*. It must not be assumed that this term indicates an infusion; many studies using intermittent bolus techniques state "continuous epidural analgesia" in the title. Inspection of the methods is required to determine which technique was used. Most importantly, infusions allow a steady dose of drug over time, thereby avoiding peaks and troughs in analgesia and side effects. Wide patient variation in response can be accommodated by titration of the rate of infusion and concentration of infusate. Side effects occur slowly over time and are easily reduced or eliminated by decreasing the infusion rate, stopping the infusion for a short time, or changing the medication in the infusion. Duration of action is no longer a factor in choosing a narcotic or local anesthetic. Morphine is used for pain over many dermatomes; meperidine, fentanyl, or other lipophilic narcotics are used for more localized pain sources. Bupivacaine is still used owing to the increased sensory blockade. Tachyphylaxis does *not* occur with continuous infusions,[102] and doses required are below those developing systemic toxicity.[74]

With medications other than morphine, analgesia with infusions is quite segmental and tends to occur only at dermatomes near the catheter tip. The rate of infusion can be varied to affect more or less dermatomes, tailoring the spread to the patient's pain source. Periodic titration with at least twice-daily checks on response is necessary; spinal canal tissue loading seems to occur over the first 8 to 24 hours with a 20 to 30 per cent decrease in dose requirement after that interval (unpublished results).

Combining local anesthetic with narcotics by infusion offers the greatest adaptability to patient needs. Total doses of either drug are reduced, along with most side effects (urinary retention being a notable exception, because it occurs with both drug classes). Patients with significant respiratory disease can have narcotics reduced in, or removed from, the infusion, reducing respiratory depression risk. In a similar fashion, patients with cardiovascular instability would receive less or no local anesthetic to avoid cardiovascular complications. The "art and science" of postoperative pain management can be maximized by this technique.

The need for infusion pumps and technical problems that occur with them (occlusions, inadequate pump pressure, line leaks/disconnects, air in the line causing automatic shut off) are drawbacks to epidural infusions. Another is the need to place the epidural catheter near the dermatomes of the pain source. Thoracic and lumbar epidural infusions tend to flow to caudal dermatomes so that the catheter tip must be near the cephalad dermatomes of the pain source to provide optimal analgesia with minimal side effects. Very lipophilic narcotics like fentanyl do not even spread as far as local anesthetics by infusion, in the author's experience. Meperidine is fairly well matched to bupivacaine spread by infusion.

Table 1 gives some guidelines for starting narcotic-only epidural infusions for postoperative pain relief in healthy patients. Table 2 includes local anesthetic (bupivacaine) with narcotic for epidural infusion. Rates of infusion must be adjusted depending on catheter placement and patient response. These guidelines must not be used in a "cookbook" fashion; patient risk factors and response require

Table 1. *Epidural Narcotic Infusions*

	MORPHINE	MEPERIDINE	FENTANYL
Initial bolus	0.03 mg/kg (~2–3 mg)	0.1 mg/kg (5–10 mg)	0.001 mg/kg (0.05–0.1 mg)
Infusion rate	0.5 mg/hr	20 mg/hr	0.075 mg/hr

Titrate both dose and volume per hour (especially with fentanyl) to achieve analgesia and dermatomal spread. Boluses of narcotics should also be in adequate volumes to achieve dermatomal spread.

titration of both types of medication and the infusion rate to achieve analgesia safely with minimal side effects.

Individual narcotics must each be carefully examined to determine their possible role in spinal analgesia. First, it must be ascertained that it does not have prolonged deleterious effects on the spinal cord or nerves in the spinal canal. At this time, the author is unaware of any reports attributing nerve or other tissue damage directly to spinal narcotics without preservatives.[29] That is insufficient reason not to use caution, however. Because all of the narcotics had previous use by other routes of administration, many FDA guidelines have been circumvented and narcotics are being applied spinally in humans when little or no data exists regarding toxicity.

Particular narcotics have features that give rise to unexpected responses when applied spinally. Mention has already been made regarding lofentanil with its high-binding affinity. Methadone, with its long half-life, was shown to develop significant plasma levels over 3 days of epidural infusion.[99] This may increase the risk of respiratory depression and other side effects with its prolonged use. Studies regarding safety, efficacy, dosage range, and preferably, pharmacokinetics, should be available before use in general practice in a nonprotocol fashion.

APPROPRIATE CASES

Patient selection for spinal analgesia should be based on significant postoperative pain at an appropriate dermatomal level or the

Table 2. *Epidural Infusions: Combination of Bupivacaine and Narcotic*

	MORPHINE	MEPERIDINE	FENTANYL
Bupivacaine 0.1%	0.005%	0.1%	0.0005%

Bupivacaine is constant but may need to start at 0.15 per cent if no concentrated bupivacaine was used intraoperatively. Similarly, initial boluses of bupivacaine and/or narcotic depends on intraoperative use and patient alertness and fluid status immediately after surgery. In *healthy* patients initially, infusion rates are 5 to 7 ml per hour for thoracic epidural infusions and 8 to 12 ml per hour for lumbar epidural infusions.

need for other benefits of the techniques. Major thoracic and abdominal cases are reasonable candidates; they may require thoracic epidural placement, however, depending on the technique and drugs used for spinal analgesia. Major vascular surgery patients may benefit from pain relief and improved vascular flow[23] if local anesthetics are used. El-Baz[32] has recommended epidural morphine infusions for open heart surgery as well. These last two applications include patients with a relative contraindication to spinal needle or catheter placement: the use of heparin or other anticoagulants. The pros and cons of spinal analgesia for these patients will be discussed later. The use of spinal analgesia for obstetrics is discussed in another article in this issue. Orthopedic procedures of the lower limb, particularly those that use continuous passive motion devices, are appropriate cases.

Depending on the philosophy and involvement of the postoperative pain service, another kind of indication presents itself. Patients with severe systemic diseases, particularly respiratory and cardiovascular, are at high risk for postoperative complications and stand to gain the most benefit from spinal analgesia. They also have the highest risk of complication from the technique itself and require extreme care and good cooperation between the pain service, surgeons, and intensive care unit team (if different from the surgeons). Respiratory care and fluid management require input from the pain service, and physicians managing cardiovascular parameters need an understanding of sympathetic blockade at various levels to appropriately adjust for its effect on the cardiovascular system. Postoperative pain service physicians should be available 24 hours a day for replacement of nonfunctional epidural catheters as well as managing difficult situations. With this kind of intensive physician input, high-risk patients such as reported by Yeager et al[103] can show marked benefits by spinal analgesia techniques; without that input, these techniques are very dangerous.

EFFICACY

Many studies have been published stating results ranging from no difference from standard parenteral analgesics to complete pain relief in all subjects. Early studies often had no randomization or blinding, and dosage choices were fairly random. Increased duration of analgesia without demonstration of improved analgesia has often been described as a beneficial result, ignoring the increased risks and increased time and expertise necessary to administer the medication spinally. Although still controversial, the author feels that epidural catheter position (with infusions or small volume bolus technique) or volume of injection by bolus can significantly affect the onset and quality of analgesia, particularly with lipophilic narcotics. This segmental effect is a well-known feature of local anesthetics in the epidural space. This effect with intrathecal application of lipophilic narcotics has not been investigated. Regarding epidural analgesia, studies with inappropriately placed catheters or inadequate volumes of injection leave some doubt as to the results obtained.

Several studies have examined analgesia and compared epidural techniques to intramuscular (IM) or IV narcotics. Analgesia is usually determined by a descriptive scale (for example, pain is very severe, severe, moderate, mild, none) or a visual analog scale (VAS) representing a "pain continuum" from zero pain at one end of the scale to very severe or "worst" pain at the other end. The VAS is usually reported in graduations up to 10 or 100. The reliability of the VAS has been documented although not specifically for postoperative pain.[82] Other investigators have used patient performance (pulmonary function tests, ambulation) to represent analgesia. None of these systems can be stated to be the best, so more than one of them may be used in a study as a cross-reference.

Another significant problem with study designs is the lack of data on dosage equivalents, either IM or IV, versus spinal, or between drugs with spinal administration. This equivalent dose data IM/IV versus spinal may not be possible at higher doses if spinal administration is actually more efficacious. Perhaps the relative equivalents of a given narcotic intrathecally should be 3.5 to 4 per cent of an epidural dose by pharmacokinetic studies.[91] This has only been demonstrated for morphine and meperidine. Chrubasik et al[21] have described a method for determining relative analgesic potency over time (not as a single bolus) of epidural narcotics. This or similar titration methods may be helpful in designs of future studies, using predetermined equipotent doses of narcotics.

Reiz et al[81] demonstrated better analgesia after hip surgery with 2 mg of morphine epidurally as compared with 10 mg morphine IM. Raj et al[73, 75] used infusions of either bupivacaine or a combination of bupivacaine and meperidine after total knee replacements. This was compared with standard surgical orders for narcotics (morphine or meperidine) IM with either epidural group having significantly better VAS scores.

After upper abdominal surgery, Scheinin et al[88] used relatively low-rate infusions of bupivacaine or morphine as compared with IM oxycodone on request and demonstrated lower VAS scores. Similar results after upper abdominal surgery have been obtained using epidural lidocaine, morphine, methadone, or hydromorphone by bolus[12] and infusion.[27] Thoracic epidural fentanyl infusions relieved pain better than IM papaveretum after upper abdominal surgery.[101]

Post-thoracotomy pain relief was significantly better with epidural morphine boluses versus IV morphine boluses, both on request.[89] Logas et al[57] compared thoracic epidural infusion (again, relatively low rates of infusion) of morphine, bupivacaine, morphine and bupivacaine, and saline to IM morphine in post-thoracotomy patients. Patients reported better relief with epidural morphine and with morphine and bupivacaine but not with bupivacaine alone when compared with IM morphine. The poor response to bupivacaine alone may have been due to low rate of infusion (3 to 6 ml per hour) or low concentration (0.1 per cent bupivacaine).

Patient-controlled analgesia (PCA) is a recent method of providing postoperative pain relief for all types of surgeries. Two recent studies[31, 40] compared epidural morphine with PCA morphine as well as IM morphine for pain after cesarean section; epidural application provided the best analgesia in both studies.

There are good studies that do not demonstrate better analgesia however. Klinck et al[51] gave epidural or IM morphine as needed to elderly patients after upper abdominal surgery and demonstrated no significant difference in VAS scores. Although Rawal et al[79] states improved analgesia with epidural morphine versus IM morphine in grossly obese patients, VAS scores do not reflect this in that study. However, by patient performance (ambulation, pulmonary function tests), pain relief was felt to be more effective with the epidural morphine. Holland et al[44] also showed no difference in VAS scores after upper abdominal surgery using a single dose of 3 mg morphine epidurally versus placebo; patients were provided IM morphine as needed for both groups.

It is the author's opinion that spinal narcotics and/or local anesthetics do provide better analgesia than conventional systemic analgesics when applied appropriately. Also, when applied appropriately, there is probably no difference in the quality of analgesia obtainable by different narcotics (complete agonists) with spinal application. Several studies[12, 21, 58, 94, 97] have demonstrated this with a variety of narcotics. Good comparative studies of partial agonists, agonists/antagonists, and specific receptor subset agonists with more standard narcotics, all by spinal application, are needed to determine the pros and cons of these narcotics. A possible "ceiling" of respiratory depression must be weighed against sedation and other side effects with them.

Comparisons of local anesthetics epidurally to narcotics (morphine in each case) have given various results. Unfortunately, many of the studies used intermittent boluses of local anesthetics, predisposing to intermittent hypotension and frequent injections. Modig et al,[60] using boluses of 0.5 per cent bupivacaine or 5 mg morphine, demonstrated better analgesia with bupivacaine "by patient report." Torda and Pybus[95] also had better VAS socres with bolus epidural bupivacaine, but another pain-score system failed to show this difference. Results by Logas et al[57] were already stated. Scheinin et al[88] reported no differences between epidural bupivacaine infusions and morphine boluses. The epidural morphine infusion group had a delayed onset of analgesia, perhaps due to a lack of any loading dose. Bupivacaine infusions patients (and other epidural groups as well) received 4 ml of bupivacaine at the start of surgery. El-Baz et al[33] compared bupivacaine bolus, morphine bolus, and morphine infusion epidurally; all three groups reported equivalent analgesia. More studies investigating combinations of narcotic and local anesthetic are needed, such as those reported by Raj et al[73] and Logas et al.[57]

BENEFITS OTHER THAN ANALGESIA

Studies investigating spinal analgesia have demonstrated several beneficial effects other than analgesia. The most consistent improvement is in pulmonary function by testing, arterial blood gases, or decreased complications. Three studies[7, 12, 95] have examined epidural local anesthetics versus epidural morphine versus control (IV or IM narcotics); all three regarding pulmonary function studies demonstrated equal and significant improvements by epidural analgesia with either type of medication. The study by Rawal et al[79] of grossly obese patients showed faster return of peak expiratory flow and fewer pulmonary complications despite equal measurements of analgesia between epidural and IM morphine. This demonstrates a pulmonary effect other than analgesia or an inadequacy of the VAS for pain measurement. Another study by Rawal et al[77] compared epidural morphine, 4 mg, with intercostal nerve block (right 6 through 11 ribs) and with IM narcotic (ketobemidone) as needed, after cholecystectomy by subcostal incision. Peak expiratory flow and arterial oxygen tension (PaO_2) were higher and arterial carbon dioxide tension lower in the epidural morphine group as compared with either of the other groups. Several other studies[89, 97, 101] have demonstrated similar improved pulmonary dynamics after thoracic and abdominal surgery with epidural narcotics. Four other investigators reported improved PaO_2 tensions with epidural local anesthetics[27, 65, 92] or narcotics[86] after upper abdominal surgery. Cuschieri et al[27] also reported significantly fewer pulmonary complications and chest infections.

Three studies have demonstrated earlier extubation with intrathecal[18, 46] or epidural[32] morphine after major abdominal or open heart surgery, respectively. An enlightening study by Catley et al[17] looked at postoperative oxygen saturation in patients receiving IV infusion of morphine or regional analgesia (epidural or intercostal nerve block with bupivacaine). Ten out of 16 patients receiving IV morphine infusions had many (456 total episodes) periods of desaturation below 80 per cent whereas none of the regional analgesia patients fell below 87 per cent. All of these episodes were during sleep. It would be quite useful to have the same study done with epidural morphine or fentanyl analgesia because epidural narcotics have been implicated regarding respiratory depression.

Modig et al[61] demonstrated decreased incidence of deep vein thrombosis and pulmonary embolism after total local anesthetics. Sympathetic block with improved blood flow as well as earlier and more vigorous ambulation have been postulated as the cause of this improved outcome. Rawal et al[79] did not find less thrombosis with epidural morphine analgesia; this could be due to the lack of sympathetic block or simply not enough patients in his study.

Sympathetic block has been proposed to improve graft and limb blood flow after vascular surgery. Cousins and Wright[23] demonstrated improved flow intraoperatively and postoperatively with epidural local anesthetics. The author is unaware of any study comparing epidural local anesthetics with epidural narcotics regarding blood flow or even a study examining patency outcome with and without postoperative epidural local anesthetics.

Several investigators have examined bowel function after abdominal surgery with the expectation that sympathetic block of the viscera would decrease postoperative ileus. Scheinin et al[88] compared epidural bupivacaine or epidural morphine with IM oxycodone (epidural groups received IM oxycodone if needed) after colonic surgery. Patients receiving epidural bupivacaine moved their bowels significantly earlier postoperatively than the other two groups (2 days versus 4 days). The study by Rawal et al[79] demonstrated earlier passage of flatus and feces in epidural morphine analgesia patients as compared with IM morphine analgesia patients. One interesting finding was larger volume of gastric aspirates in the epidural group; this corroborates an earlier study by Nimmo et al[67] in post-hysterectomy patients. Thoren and Wattwil[93] demonstrated in volunteers that this effect is caused by epidural morphine, not by an equal dose IM, and not by thoracic epidural bupivacaine. Not all studies have demonstrated the decreased gastrointestinal transit time despite well-designed, well-controlled studies.[43, 98]

The study by Yeager et al[103] in high-risk surgical patients used epidural analgesia (local anesthetics or narcotics at the discretion of the pain service) versus parenteral systemic narcotics and demonstrated a decrease in overall morbidity and mortality in the epidural groups. These patients also had a shorter ICU and hospital stay. Several other studies[46, 71, 79] have demonstrated a shorter hospital stay in patients receiving epidural analgesia. This may ultimately be the moving force for acceptance of epidural analgesia among the medical community and third-party payors.

The effect of regional anesthesia and analgesia on the stress response during and after surgery has been a controversial subject for some time. Several markers of the response have been investigated: glucose, free fatty acids, cortisol, catecholamines, nitrogen balance, insulin, glucagon, antidiuretic hormone, growth hormone, and prolactin levels. Results of available reports are often confusing and contradictory. Kehlet has written an excellent review on the subject,[50] and most of the following interpretations are from that review.

Local anesthetic intrathecal or epidural block has a significant effect on the catecholamines (decreased plasma and urine levels) without surgical stimulus[72]; spinal narcotics alone have not been studied. Spinal local anesthetics have a greater efficacy in obtunding the stress response to surgery than spinal narcotics, although both do have an effect.[19, 39, 85] Unless the spinal local anesthetics are administered prior to starting surgery, much of the stress-response blocking effect is lost.[62] The stress response from upper abdominal surgery has been harder to block or modify than that from lower abdominal surgery[52] for as yet unknown reasons.

The theory behind this research is that, with modern advances in surgery and postoperative care, the natural stress response is detrimental rather than beneficial.[49] If true "stress-free surgery" can be performed, then perhaps outcome studies and cause-effect relationships can be established regarding this theory. As of now, the stress response after 24 to 48 hours has not been signficantly modified by these techniques.

COMPLICATIONS

Whenever an invasive technique is employed, possible complications ensue. These complications may be because of the technique itself or the medications employed. Intrathecal injections or epidural attempts with dural puncture may cause post-dural puncture headaches or, rarely, meningitis. In the thoracic region, the spinal cord can be damaged by an epidural needle as well; this has also been a very rare event. Back pain and muscle spasm in the area of the procedure are not uncommon, but they usually resolve in a few days to a week. Placement of an epidural catheter runs the risk of infection from a foreign body in the epidural space. This manifests itself as an epidural abscess or meningitis, particularly rare in postoperative pain management. This has become more prevalent with long-term catheters in immunocompromised cancer patients. Bleeding can result in epidural or subarachnoid hematoma with serious permanent neurologic sequelae. Two large studies of 4011[76] and 1000[68] patients receiving IV heparin after epidural or intrathecal block for surgery had no cases of epidural or subarachnoid hematoma. They do cite several case reports of this happening, however. If patients are to receive anticoagulants (or are already receiving them as in Odoom's study,[68] an understanding of risks versus benefits must be established both with the patient and the surgeon.

Another interesting complication is migration of the catheter after placement. The catheter can migrate out of the epidural space (inadvertently pulled back into the interspinous area or advanced through an intervertebral foramen) resulting in loss of analgesia or, if local anesthetics are used, unilateral analgesia of significantly decreased dermatomal spread. The catheter can also migrate intravascularly or transdurally (subdural or subarachnoid). All of these sequelae have occurred on the author's service (unpublished results) and at least two reports of subdural migration have been submitted.[16, 41]

The response to IV or transdural migration depends on the drugs employed and the method of administration. Bolus administration of local anesthetics or narcotics IV causes possible systemic toxicity or rapid systemic effects, respectively. Aspiration of the catheter or holding the injection site below the level of the catheter tip may indicate the migration (IV or transdural), but this is not universally effective, particularly with subdural migration. Infusion technique with IV migration results in loss of analgesia *without* systemic toxic or exaggerated effects because epidural absorption over time is equal to IV infusion levels at steady state. Transdural migration results in exaggerated response (and side effects) by bolus or infusion with local anesthetics or narcotics. Any combination can lead to early or delayed complications with delayed response to bolus local anesthetics being the least likely. In the author's experience, these transdural migrations with infusion technique have not lead to permanent sequelae, but sedation and respiratory depression (with narcotics) and hypotension and increased motor block (with local anesthetics) have occurred.

Another problem is inappropriate placement of the catheter initially in an ineffective tissue. The incidence of this depends on the experience of the anesthesiologist and compulsive testing of the catheter placement. Patients will be extremely unhappy with a service that does not provide analgesia and restricts administration of systemic narcotics.

Spinal narcotics have demonstrated the following difficulties during postoperative pain management: respiratory depression, sedation, nausea and vomiting, pruritis, and urinary retention. A separate article in this text is devoted to respiratory depression. Opioid withdrawal syndrome is a possible problem in narcotic-tolerant patients, but has only been reported in cancer patients so far.[20, 59, 96] The use of a partial agonist or agonist-antagonist may increase this risk.[25]

Sedation is a side effect that may or may not be accompanied by respiratory depression. Many studies comparing spinal with systemic narcotics have noted decreased sedation with spinal application,[31, 51, 58, 101] although sedation is clearly a possible effect of spinal narcotics.[8, 12] Sedation may be increased with narcotics demonstrating higher ratios of epidural to systemic effective analgesic dose such as sufentanil[28] and with the use of kappa-selective agonists and partial agonists (personal communications, animal work by Lander[53]). The tendency for kappa agonists to result in increased sedation with epidural use may be due to less potency for somatic pain and analgesia while having equivalent sedation effects.[104]

Nausea and vomiting has been observed in volunteers receiving epidural morphine[15] but its relation to postoperative pain relief is less clear. There is approximately a 30 per cent incidence of nausea and vomiting in postoperative patients receiving systemic narcotics[25] and several studies have demonstrated an equal[40, 51, 54] or lower[31, 81] incidence of this side effect with spinal narcotic analgesia as compared with systemic narcotics. If nausea and vomiting from epidural narcotics are a problem with a given patient, this problem is reversed by naloxone, often without altering satisfactory analgesia.[25] However, naloxone administration is not without risk, including acute pulmonary edema[35] and sudden death,[4] so its administration should be used with caution and for good reason rather than prophylactically.

Pruritis can be a significant problem to patients receiving spinal narcotics, particularly with morphine. The incidence has been reported as anywhere between 1 per cent[81] and 100 per cent.[6] Although comparative information is minimal,[34] fentanyl seems to cause a relatively high incidence as well, with other narcotics causing some lesser percentage of pruritis. Although the cause is unknown, it is not thought to be due to histamine release, despite usually effective treatment with diphenhydramine. Naloxone has also been effective.[15] Quite often changing the narcotic is helpful in decreasing or eliminating pruritis as well.

Urinary retention occurs with narcotic administration by any route, but is more frequent and pronounced with spinal administration. Rawal et al[78] demonstrated bladder detrusor muscle relaxation as the major cause of retention and stated arguments for both pontine and spinal sites of opiate action. This study also demonstrates reversal of this effect by naloxone infusion. A recent study in rats receiving intrathecal morphine[30] demonstrated complete loss of the micturition reflex with consequent inability to relax sphincter tone as well. Cholinergic drugs (carbachol, bethanechol) worsened the intravesical pressure, whereas apomorphine (a dopamine agonist) was particularly effective in reducing retention and restoring the micturition reflex. Urinary retention (and pruritis) is particularly disturbing to patients. If catheterization is required, it becomes disturbing to surgeons as well because of the risk of infection.

Certain side effects of narcotics have yet to be reported or proved with spinal administration. Chest wall or glottic rigidity is a known complication of fentanyl and other high-potency narcotics but has not been reported with spinal administration. Rudy and Yaksh[84] and Adler et al[1] describe alterations in temperature regulation from central effects of opioids; this has not yet been shown to occur, but might require large numbers of patients because of wide temperature swings in postoperative patients. Dysphoria has been reported as a consistent response to kappa receptor specific narcotics,[70] but reports of their use spinally have not demonstrated this. Further use of spinal narcotics may or may not show these theoretical problems to be significant.

Many patients may have on their charts or will tell you that they are allergic to one or more narcotics. This is usually nausea, nonspecific histamine release, or dysphoria, but a true allergic response to a narcotic (or local anesthetic) is possible. This is very rare with preservative-free narcotics or local anesthetics (particularly amide local anesthetics such as bupivacaine).

Complications from local anesthetic spinal analgesia are fairly straightforward: hypotension, motor block, urinary retention, and systemic toxicity. As mentioned previously, periodic boluses run the risk of repeated episodes of hypotension with each injection and have been significant occurrences with this method.[33, 47, 60, 90] In the author's experience, most patients receiving epidural bupivacaine infusions can maintain an adequate blood pressue by titrating the infusion rate and maintaining adequate IV fluids in the early postoperative period. A few patients will not tolerate the sympathetic block of even a low-rate, low-concentration bupivacaine infusion, and the infusion must be discontinued or changed to narcotic only.

Infusions are also required to avoid intermittent motor block, particularly with lumbar catheters. A certain amount of intercostal and abdominal wall motor block is well tolerated in all but the severest lung disease patients, but leg weakness from a lumbar infusion can stop early ambulation, decreasing the benefit of the epidural. Even with infusions, some patients will not achieve adequate analgesia without sufficient local anesthetic to cause motor block. It is important to note that patients who develop significant motor block for any length of time are at risk for developing decubiti on their sacrum, heels, and any other pressure point. If such a strong block is to be maintained, the patients need to be on a sheepskin or "eggcrate" mattress (or one of the more specialized beds for immobile patients) with heel protectors, moved frequently, and consistently observed to avoid other pressure points from position.

Urinary retention is a frequent side effect (as much as 80 per cent of patients[45]) that does not seem to decrease with infusions and is increased by narcotics added to the infusion. Thoracic placement may decrease the incidence but most patients requiring thoracic catheters have urinary catheters placed per surgical routine. This makes the incidence difficult to assess.

Systemic toxicity to local anesthetics usually results from IV injection with rapid high serum levels as stated in the pharmacokinetics section of this article. Other than nervous system toxicity, bupivacaine (and perhaps etidocaine) can cause cardiac arrhythmias and even cardiac arrest, which has been reported to be refractory to resuscitation.[3] Recommendations have been to limit boluses to 25 to 30 mg of bupivacaine at a time, waiting 1 to 2 minutes (if a larger total dose is needed) to see if signs of toxicity develop.

MONITORING

With any patient risk, the question of assessment and monitoring must be raised. Many anesthesiology departments are currently using spinal analgesia techniques only in intensive care settings[64] as suggested by Bromage.[13] However, a significant number of services allow patients receiving spinal analgesia to be on regular wards.[64] This is a decision that must be made by anesthesiology, surgery, and hospital administration (with risk management), looking at the needs of the patient population and the medicolegal "climate" of the area. At the author's institution, this service has been offered since 1979 for approximately 2000 patients; the use of epidural analgesia has not been a consideration for placement of patients in intensive care or on wards. Patients receiving epidural narcotics have respiratory rate checks every hour for 24 hours after starting the infusion. This has proved safe in our experience.

Many mechanical respiratory monitors have been designed and marketed for spinal analgesia in patients. The ideal monitor would measure minute ventilation without being cumbersome to the patients and with few "false alarms." The available monitors fall short of this.

Motion gauges under the patient or bed mattress, strain gauges around the abdomen or chest, and impedance monitors all measure attempts at ventilation whether effective air exchange occurs or not. Pulse oximetry (particularly in patients receiving supplemental oxygen) is a fairly late measure of apnea and several of the sensors are easily knocked out of position; cold patients often do not register appropriately. Expired CO_2 monitors also easily get dislodged or plugged by secretions. Patient's breathing patterns change from mouth to nose intermittently, registering apnea incorrectly from some sampling catheters depending on placement. This is not meant to say that these monitors are of no value; each can improve detection of respiratory insufficiency over no monitor at all. However, those caring for the patient must not rely on these monitors exclusively. Also, when monitors frequently false alarm, nurses soon learn to ignore them (as anyone would), and their effectiveness is lost.

SUMMARY

The use of spinal (epidural or intrathecal) narcotics and local anesthetics for postoperative analgesia is becoming popular. The pharmacokinetics and pharmacodynamics of spinal narcotics are very important to determine dosage and intervals with bolus administration. Less lipid-soluble narcotics have slower onset, greater dermatomal spread, and longer duration of action than more lipid-soluble narcotics. Certain specific narcotics have unusual features affecting their use. Bupivacaine is the local anesthetic of choice for epidural analgesia, but lidocaine and others have been used successfully.

Both bolus and infusion technique can be used for a given practice. Epidural rather than intrathecal techniques are needed to provide analgesia consistently for more than 24 hours.

Many surgical cases are appropriate for spinal analgesia; both analgesia and other benefits (for example, sympathetic block, improved pulmonary function) need to be considered. Spinal analgesia for intensive-care critically ill patients can be very beneficial but requires extensive follow-up.

Both narcotics and local anesthetics by spinal application have been shown to be an improvement over most "standard orders" for analgesia, pulmonary function, and hospital stay; other possible benefits are less certain or specific to technique and surgery. Possible complications are extensive and require consistent physician monitoring of patient response.

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Non-narcotic Modalities for the Management of Acute Pain

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There was an age in medical practice when the physician concerned himself solely with diagnosis and treatment.[249] The rendering of pain relief per se, that is, symptom management, was not a proper pursuit for the 19th century physician, since correct diagnosis and treatment, it was felt, should lead to resolution of symptoms, including pain. In the special situation of labor pain, such analgesia was felt to be immoral and contrary to the divine mandate, "in pain shall you bring forth children" (Genesis 3:16). As medical practice and social attitudes have evolved, so has the role of the physician in providing analgesia for acute pain. As detailed in the article by Yeager in this issue, the concern for relief of such pain is a concern for reducing morbidity. The pathophysiologic consequences of acute pain involve multiple organ systems with alterations in neuroendocrine function, respiration, renal function, gastrointestinal activity, musculoskeletal function, circulation, and autonomic nervous system activity. Inadequately treated pain may result in cardiac arrhythmias, hypertension, and myocardial ischemia, with disastrous consequences. Postoperative pain is a unique acute pain situation in which the pain itself is largely iatrogenic. The physician is obliged in this circumstance to minimize the adverse effects of the pain from tissue trauma for which he is responsible.

MECHANISMS AND MODES: THE STRATEGY OF ACUTE PAIN MANAGEMENT

An appreciation of the physiologic mechanisms of pain and knowledge of modes of action of analgesics, as well as the modalities of clinically administering such analgesics allows one to formulate strategies in managing various acute pain situations. Pain pathways and mechanisms are discussed in the article by Sorkin in this issue; but

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as a means of organizing the present discussion, consider that acute pain results from activation of nociceptors responsive to a variety of pain-provoking stimuli. Pain transmission occurs along peripheral nerves and spinal cord tracts; descending modulation of pain occurs at multiple levels within the CNS from such sites as the midbrain and the dorsolateral funiculus; and thalamus and sensory cortex form the substrates of pain awareness and appreciation.

Our current pain management techniques permit intervention at a number of sites within this pain transmission/pain modulation system. For example, nociceptors within denuded skin or irritated mucosal surfaces may be anesthetized with topical agents; wounds may be perfused or infiltrated with local anesthetic solutions. Peripheral nerve blocks, plexus blocks, spinal, caudal, and epidural anesthesia are regional techniques that all involve interruption of the pain transmission system. On the other hand, pain modulatory systems are activated with the administration of stimulation techniques such as acupuncture and transcutaneous electrical nerve stimulation. Narcotic analgesics invoke endogenous pain control systems operant within the spinal cord as well as the brain. Central appreciation of pain is modified by inhalational anesthetics and a variety of other pharmacologic agents and nonpharmacologic techniques.

The approaches to management of acute pain can be quite diverse, as suggested previously. Additionally, the existence of multiple routes of administration of systemic medications (for example, inhalational, oral, intravenous, intramuscular, rectal, sublingual, transdermal, intranasal) and local anesthetics (for example, topical, perineural, perivascular, epidural, interpleural) provide the clinician with many techniques and combinations of techniques for administering analgesia. Rational selection of techniques for managing a particular situation depend on the etiology of the pain as well as the constraints of the clinical situation. The remainder of this article is devoted to reviewing non-narcotic modalities for the management of acute pain. The diversity of these techniques can be well appreciated, underscoring the broadening of our knowledge of pain mechanisms and our ever-growing armamentarium of options for providing analgesia.

INHALATIONAL ANALGESIA

Since the description of nitrous oxide analgesia by Sir Humphry Davy in 1800,[54] inhalational agents have been employed for analgesia in surgery, dentistry, and obstetrics. The ability of such agents to render a patient insensible to the pain of surgical procedures spawned the age of modern surgery. Evolving clinical practices restricted the use of most inhalational anesthetics to the operating theater, although certain of these agents, administered in subanesthetic concentrations, continued to see considerable use outside of the operating room as analgesic agents. These included such agents as cyclopropane, chloroform, methoxyflurane, trichloroethylene, and nitrous oxide.

Volatile Inhalational Agents

The use of such agents is largely of historical interest now, although as recently as within the past two decades methoxyflurane and trichloroethylene continued to be used for obstetric and postoperative analgesia. Such devices as the Cyprane and Emotril inhalers and the Penthrane Analgizer provided low inspired concentrations of volatile agent diluted in air, and their simplicity permitted use outside of the operating room. Additionally, these devices were quite suitable for patient self-administration. Methoxyflurane, intermittently self-administered, was deemed to be a safe and convenient means of providing analgesia during delivery.[73, 145] However, concerns about the potential for nephrotoxicity of methoxyflurane as well as the risks of poorly supervised administration of this agent, the potential for excessive obtundation because of the decreased anesthetic requirement of the gravid parturient, loss of airway reflexes, and gastric aspiration have virtually eliminated the use of this agent for obstetric analgesia in this country. The practice of regional analgesia has largely supplanted inhalational analgesia for obstetric deliveries. Trichloroethylene, which saw some use in providing postoperative analgesia,[105] particularly in conjunction with postoperative physiotherapy,[70] fell from clinical use owing to its instability in soda lime and the neurotoxic potential of its degradation products, as well as the concern for the carcinogenic potential of this agent.[11]

Nitrous Oxide

By contrast, the use of nitrous oxide analgesia still persists. A 1986 survey of obstetric practices in the United States revealed that of more than 1000 hospitals surveyed, the administration of nitrous oxide analgesia for vaginal deliveries was common in about 6 per cent of these hospitals.[90] In the United Kingdom, use of nitrous oxide analgesia for this indication is far more widespread and is not confined to the delivery suite. Intermittent inhalation of Entonox (50 per cent nitrous oxide and 50 per cent oxygen in premixed cylinders) is employed not only for obstetric deliveries, but for surgical dressing changes, analgesia for road transport of trauma victims, and analgesia in the immediate postoperative period as well (H.A. Noble, 1988, personal communication). Painful procedures such as postsurgical physiotherapy, orthopedic manipulations, and wound care are typically managed with intermittent Entonox inhalation.[16] Midwives, ambulance personnel, and recovery room nurses are trained in its administration in the United Kingdom. Entonox is felt to be a safe mixture of nitrous oxide and oxygen, minimizing risks of hypoxia and inadvertent over-anesthetization of most patients,[45] although the somnolent head trauma victim and the intoxicated ambulance patient would be among the obvious exceptions to this.

The continuous postoperative administration of nitrous oxide by face mask or by nasal cannula for up to 48 hours has been described.[122, 183] In addition to providing analgesia, improvement in postoperative vital capacity[179] and functional residual capacity have been reported.[122] The duration of exposure to nitrous oxide must be limited because of its ability to impair methionine synthetase activity, thereby interfering with folate metabolism and DNA synthesis.[171] The result of this is bone marrow depression and leukopenia,[127] which accompanies chronic nitrous oxide exposure. For this reason, monitoring of blood counts is recommended when nitrous oxide administration exceeds a 24-hour duration.[183] There may be an increased risk to the patient who is already immunocompromised.

Chronic trace-level nitrous oxide exposure may represent a potential hazard to health care personnel, although the significance of this is still debated. Methionine synthetase activity in rodents is decreased after prolonged exposure to nitrous oxide in a concentration of 1000 ppm but not 450 ppm.[170] The 1977 NIOSH standard for environmental nitrous oxide is 25 ppm, which is well met by current practices in operating room ventilation and use of scavenged anesthetic systems and cuffed endotracheal tubes. The use of nitrous oxide outside of the operating room, even when demand-breathing systems are employed, may result in substantially higher environmental concentrations because the patient exhales directly to the atmosphere. Nasal cannula nitrous oxide delivery systems may vent nitrous oxide to the atmosphere at rates as high as 5 L per minute,[122] which may exceed the ability of room ventilation to maintain the recommended NIOSH levels of trace gas (depending on number of patients receiving nitrous oxide, room size, and room air exchange rate). The use of isolation facilities may be appropriate for patients receiving such therapy, but such a constraint would certainly limit the widespread use of this modality for postoperative analgesia.

INTRAVENOUS ANALGESIA

By far, the most extensively used intravenous analgesic agents are the opiates. The advent of patient-controlled on-demand narcotic infusions has advanced the practice of administering intravenous narcotic analgesia immeasurably. Aspects of opiate pharmacology, opiate analgesia, and patient-controlled analgesia are detailed in other articles in this issue. The present discussion will focus on intravenous non-narcotic agents that have been examined for their analgesic properties.

Ethyl Alcohol

Intravenous ethyl alcohol has received some attention in the past as an anesthetic and analgesic agent, although interest in this particular modality has alternately waxed and waned. Some of the earliest medical applications of intravenous ethanol, in the 1920s, included postoperative sedation and surgical anesthesia,[64] and its applicability as a tocolytic agent was reported later by Fuchs.[86] Certain features made intravenous ethanol infusions an attractive technique for providing general anesthesia, such as the remarkable degree of hemodynamic stability observed, its synergism with adjunctive agents such as barbiturates and narcotics, its ability to maintain urine output (via inhibition of antidiuretic hormone), its elimination by oxidative metabolism, and its ability to provide sedation and analgesia in the postoperative period without respiratory depression.[64, 153, 209] Its ability to induce peripheral vasodilation made it a useful technique for inducing hypothermic anesthesia,[64] and anecdotally was observed to improve tissue perfusion in diabetic gangrene[18] and relieve anginal symptoms through a putative coronary vasodilatory action.[26, 209] As an analgesic agent, Behan reported that 80 per cent of patients who had received intravenous ethanol postoperatively experienced no pain or only slight pain.[18] Analgesia to experimentally induced pain in volunteer subjects receiving 1.5 ml per kg of 10 per cent ethanol in saline intravenously was reported by James and coworkers, and the elevation in pain threshold was seen to be comparable to that of 0.2 mg per kg of morphine.[110] Other investigators have felt that the analgesic action of ethanol alone was not quite satisfactory,[209] and that its main usefulness was as an adjunct to narcotic therapy, being an excellent potentiator of opiate analgesia,[26] thus reducing the total narcotic dose required to achieve pain relief. Consistently reported side effects that have limited the popularity of intravenous ethanol in clinical practice have been its propensity to induce emergence delirium, headache, nausea, vomiting (that is, hangover), and venous thrombosis.[51, 64]

Intravenous Local Anesthetics

Intravenous local anesthetic infusions are of both historic as well as current interest, as an adjunct to general anesthesia and as a means of alleviating acute and chronic pain. The earliest studies of the effects of intravascular local anesthetic administration were conducted in the late 19th and early 20th centuries; Leriche detailed the use of such infusions in treating painful vasospastic states.[138] As adjuncts to general anesthesia, infusions of procaine and lidocaine have been used for supplementation of thiopental anesthesia and inhalational anesthesia since the 1940s. Himes and associates studied the effects of intraoperative lidocaine infusions on anesthetic requirement for nitrous oxide and halothane and found a lowering of anesthetic requirement related to serum concentration of lidocaine in both human and animal subjects.[102] As a general anesthetic adjunct, lidocaine seems capable of contributing a maximum MAC equivalent of 0.4,[57] and in humans a lidocaine plasma level of 3.2 μg per ml is estimated to provide approximately 1 MAC when administered with 70 per cent nitrous oxide.[102]

In 1943, Gordon reported on the analgesic effects of intravenous procaine in burn patients.[95] During that same period, intravenous procaine was evaluated favorably as an obstetric analgesic[102] and as a postoperative analgesic.[139] Studies conducted since then have consistently noted diminished pain scores and narcotic requirements in the postoperative period[14, 39, 240] in patients receiving intravenous lidocaine infusions. Additionally, Wallin and coworkers noted a decreased incidence of hypertension and tachycardia following extubation and a lowered urinary catecholamine output on the second and third postoperative days in lidocaine-treated patients.[240]

Various chronic neuralgic pain states, such as deafferentation pain, tic douloureux, and painful diabetic neuropathy have been benefited by the infusion of 2-chloroprocaine[208] and lidocaine.[25, 26, 67, 97, 114] Perception of experimentally induced pain has also been reported to be attenuated by intravenous local anesthetics. Elevation in cutaneous pain threshold to radiant heat was observed in volunteer subjects following procaine administration;[22] the effect was reportedly comparable to that of 300- to 600-mg doses of aspirin. The effect of intravenously administered lidocaine on tolerance to tourniquet-induced ischemic pain appears to be related to plasma concentration. A critical blood level of 3 μg per ml is apparent, below which no analgesic effect is seen.[25, 202]

The mechanism by which systemically administered lidocaine produces analgesia is still the subject of some speculation. Hypotheses have been proposed that implicate the peripheral sensory apparatus (nociceptor, primary afferent neuron) as well as the CNS (spinal polysnyaptic pathways, supraspinal sites of action). The transudation and preferential accumulation of systemically administered local anesthetic in traumatized tissue has been proposed,[4] which implies a local site of action. However, a direct conduction block is not likely at clinically relevant concentrations. Woolf and Wiesenfeld-Hallin demonstrated this in rats receiving systemically administered local anesthetics (lidocaine and tocainide);[249] however, in spite of preserved impulse conduction in primary afferents, there was a marked attenuation in C-fiber evoked polysynaptic withdrawal reflexes, suggesting a more central site of action of these drugs. On the other hand, a possible prostaglandin-inhibitory effect of local anesthetics has been proposed,[104] which is consistent with the observation that lidocaine is capable of preventing the characteristic inflammatory changes of peritonitis.[40, 138] Because prostaglandins sensitize peripheral nociceptors to painful stimuli (see the following discussion on prostaglandin inhibitors), an overall reduction in pain sensation would be expected as a result of local anesthetic-mediated prostaglandin antagonism. This would be comparable to the reduction in pain seen with nonsteroidal anti-inflammatory drugs. It is interesting to note that both of these classes of medication seem to have a ceiling effect in the setting of acute pain.

Ketamine

A third intravenous analgesic agent worthy of note here is ketamine, an arylcycloalkylamine compound introduced into clinical practice in 1965 as an intravenous "dissociative" anesthetic.[60] The potent analgesic effect of ketamine was quite obvious even in this initial report. The usefulness of ketamine as an anesthetic in burn surgery became apparent shortly after this time.[24, 50] It was also reported during this same period that ketamine, administered in doses (0.4 mg per kg IM) less than that required to produce anesthesia, that is, subdissociative doses, produced an elevation in threshold to experimentally produced pain comparable to 1 mg per kg IM of meperidine, although of somewhat shorter duration; the same dose also provided satisfactory postoperative analgesia lasting about an hour in 80 per cent of surgical patients receiving the drug.[205] Additional reports verified the production of clinically useful analgesia of subdissociative ketamine doses in a variety of settings.[43, 44, 219] In an effort to extend the duration of analgesia, subsequent investigators examined the effect of continuous intravenous infusions of ketamine on postoperative pain.[42, 109, 176] Each of these investigators noted the production of analgesia, though somewhat less profound when compared with narcotic analgesia, but with significant sparing of respiratory drive. The clinical response to ketamine is dependent on plasma levels achieved, analgesic levels being in the range of 100 to 150 ng per ml and anesthetic levels being 650 ng per ml and greater.[43, 44] For production and maintenance of analgesia, an infusion of 3 to 4 μg per kg per minute following an intravenous bolus of 1 mg per kg has been suggested.[160] When studied clinically, this infusion rate was found to produce postoperative analgesia comparable to that produced by 33 μg per kg per minute of morphine, without a comparable reduction in ventilation.[176]

The mechanism of ketamine analgesia has been the subject of a considerable amount of investigation. Numerous neuromodulatory systems may be involved, and the state of ketamine analgesia may be quite a separate and distinct phenomenon from that of dissociative anesthesia. Domino and associates noted in their original report[60] that the high amplitude theta wave activity that characterized the state of dissociative anesthesia disappeared when their subjects regained consciousness and became conversant, although analgesia was still present, and normal alpha activity did not return until some time after the analgesic effect had subsided. Case reports of patients with cortical disease who had failed to demonstrate analgesia to surgical stimuli in spite of multiple doses of ketamine suggested that an intact and functioning neocortex is a prerequisite for ketamine analgesia.[62, 111, 155] Animal studies have confirmed a dual contribution of supraspinal and spinal sites of action in production of ketamine analgesia, and their relative contributions may depend on the particular dose range studied.[46, 119, 174] The production of analgesia following periaqueductal gray administration of ketamine and its antagonism by naloxone suggested an opiate mechanism of ketamine analgesia,[98] and a direct opiate receptor effect of ketamine was reported initially[221] but later refuted.[93, 222, 244] However, the possibility of an *indirect* enkephalinergic effect of ketamine mediated by release of endogenous opioid peptides cannot be excluded.[84] A sigma-opiate receptor (phencyclidine receptor) effect has been described of ketamine, but this is not known to mediate analgesia. Still other work has suggested an effect of ketamine on serotonin turnover,[144, 237] and analgesia produced by intrathecal ketamine has been shown to be reversible by methysergide, a serotonin antagonist.[234] It is therefore conceivable that different neurochemical mechanisms may be operant at the spinal and supraspinal levels in the production of ketamine analgesia.

Widespread acceptance of the use of ketamine has been tempered by the concern of emergence delirium and hallucinatory phenomena. Such effects are observable following subdissociative doses[89, 109, 176, 205] as well as full anesthetic doses,[241] and are frequently but not always an unpleasant experience.[99, 120, 176, 194, 205, 242] Adjunctive medications such as diazepam,[65] droperidol,[71, 204] physostigmine,[12] lorazepam,[132] and midazolam[190] are reported to be capable of attenuating the adverse psychological sequelae of ketamine, and proper patient selection may be prudent.[89, 99] Another concern with regard to extended use of ketamine is the potential for tolerance,[24, 113, 219] although this phenomenon is usually described in the context of repeated doses rather than continuous infusions and may not preclude its short-term use in the postoperative period.

The epidural administration of ketamine is discussed later in this article. Other intravenous agents are discussed under subsequent headings as well; in particular, the intravenous administration of nonsteroidal anti-inflammatory agents is discussed in the next section.

PROSTAGLANDIN INHIBITORS

Nonsteroidal anti-inflammatory agents, comprising a family of chemically diverse compounds (Table 1), are typically considered to be mild analgesics, useful in a variety of clinical situations such as the treatment of inflammatory and degenerative joint disease, myalgias, headache pain, and dysmenorrhea. Their antipyretic effects and platelet-aggregation inhibiting effects are likewise useful. In the treatment of more severe pain disorders, they are frequently bypassed, however, in preference of the more potent narcotic analgesics. A more circumspect regard for the mechanisms of pain and an understanding of the phenomenon of hyperalgesia resulting from trauma and inflammation permits one to acknowledge a proper role for nonsteroidal anti-inflammatory analgesics in the management of acute pain.

Mechanisms of Action

Hyperalgesia is the intensification of or sensitization to painful stimuli; this occurs as a result of the lowering of the threshold of nociceptors that have become sensitized by the release of inflammatory mediators as a result of trauma and tissue damage,[78] a form of biological amplification of the pain stimulus. Mediators of inflammation that are known to sensitize peripheral nociceptors include the prostaglandins, the metabolic products of arachidonic acid that result from the activity of the enzyme cyclo-oxygenase. Nonsteroidal anti-inflammatory medications are felt to produce analgesia by virtue of their ability to prevent the elaboration of prostaglandins, thereby preventing nociceptor sensitization and lowering the appreciation of pain. Hence

Table 1. *Nonsteroidal Anti-inflammatory Agents by Classes*

ACIDIC AGENTS			NONACIDIC AGENTS
Carboxylic acids	*Alkanoic acids*	*Enolic acids*	
Salicylates	Propionic acids	Oxicams	p-aminophenols
Aspirin	Ibuprofen	Piroxicam	Acetaminophen
Lysine acetyl salicylate	Naproxen		Phenacetin
	Fenoprofen	Pyrazolidinediones	
Diflunisal	Indoprofen	Phenylbutazone	Pyrazoles
Choline magnesium trisalicylate	Suprofen	Oxyphenbutazone	Dipyrone
	Benoxaprofen		Isopyrone
	Indole/indene acetic acids		
Fenamates			
Meclofenamate	Indomethacin		
Mefenamic acid	Sulindac		
Flufenamic acid			
	Aryl acetic acids		
	Alclofenac		
	Diclofenac		
	Fenclofenac		
	Heteroaryl acetic acids		
	Tolmetin		
	Zomepirac		
	Ketorolac		

the primary role of this class of compounds is quite different from that of opiates, which *inhibit* afferent nociceptive impulses at such sites as the dorsal horn; or neurally applied local anesthetics, which directly *interrupt* impulse conduction; rather, these compounds prevent the amplification of nociception, which seems to accompany inflammation and tissue trauma.

The inhibition of prostaglandin synthesis, described by Vane nearly two decades ago,[236] forms a cornerstone in our understanding of nonsteroidal anti-inflammatory analgesics. This class of analgesic compounds, by inhibiting the action of cyclo-oxygenase, blocks the production of arachidonic acid metabolites, of which prostacyclin (PGI_2) and prostaglandins E_1 and E_2 (PGE_1, PGE_2) are well recognized for their ability to induce hyperalgesia.[78] However, additional observations betray the complexity of inflammatory-mediated hyperalgesia and of the mechanism of action of these analgesic compounds:

1. The nonsteroidal anti-inflammatory agents are classically regarded as peripherally acting analgesics.[133] However, the analgesia resulting from prostaglandin inhibition is not a purely peripheral phenomenon. There is evidence that prostaglandins exert hyperalgesic effects within the CNS at spinal and supraspinal sites.[77]
2. Hence, a medication such as acetaminophen, which possesses poor anti-inflammatory properties, is nonetheless antipyretic and analgesic. Acet-

aminophen exerts a much greater degree (an order of magnitude greater) of prostaglandin inhibition within CNS tissue than in peripheral tissue. By comparison, indomethacin exerts relatively greater peripheral than central prostaglandin inhibition and aspirin exerts approximately similar degrees of prostaglandin inhibition within the CNS as well as peripheral tissues.[81]

3. The nonacetylated salicylates such as diflunisal and magnesium trisalicylate do not block cyclo-oxygenase as does aspirin; and yet these compounds inhibit prostaglandin activity. Hence, it may be necessary to postulate another mechanism of action. It has been reported that nonsteroidal anti-inflammatory agents are membrane-stabilizing compounds, and that their analgesic activity correlates with their respective octanol/water partition coefficients; in this way these compounds may prevent prostaglandin release by a membrane-specific effect,[253] cyclo-oxygenase inhibition would then not be a prerequisite for analgesic activity.
4. It has also been suggested that other diverse compounds such as local anesthetics, tricyclic antidepressants, and methylxanthines, by virtue of membrane stabilization, may be prostaglandin inhibitors as well.[104]
5. Arachidonic acid is also metabolized by the enzyme lipoxygenase to form an additional group of inflammatory mediators, the leukotrienes. Leukotriene B_4 is known to produce hyperalgesia.[131] Hence, the most useful analgesics may be those producing dual inhibition of lipoxygenase as well as cyclo-oxygenase. Benoxaprofen is one such compound[150] but unfortunately most compounds available for clinical use are not lipoxygenase inhibitors, and may be therefore limited in this respect.

Nonsteroidal anti-inflammatory agents are not true prostaglandin antagonists because exogenously administered prostaglandins will exert their effects even in the presence of these anti-inflammatory agents;[16, 75, 96, 223] rather, these agents are limited to the prevention of the de novo release of endogenous prostaglandins. Prostaglandins that have already been released continue to exert their hyperalgesic effects for a finite period of time. Hence, in the setting of pre-existing tissue trauma, inflammation, pain, and hyperalgesia, the analgesic effect of a nonsteroidal anti-inflammatory may not become apparent until previously released inflammatory mediators have ceased their activity. This is relevant when one considers that PGE_2 is known to have a relatively long duration of action whereas the hyperalgesia induced by PGI_2 is of brief duration.[101] This may explain the apparent delayed analgesia of nonsteroidal anti-inflammatory agents given for chronically painful inflammatory conditions.

In consideration of the above, it may appear logical to administer these medications prophylactically when tissue trauma is anticipated, and *before* release of inflammatory mediators occurs; for example, in the preoperative period. Although many investigators have evaluated the efficacy of such medications in the treatment of postoperative pain, relatively few have considered administering such medications preoperatively. The concept of prophylaxis with such agents has only recently been examined. The prophylactic effect of indomethacin administered prior to eye surgery was found to prevent release of PGE_2 into aqueous humor;[121] this would presumably minimize the inflammatory sequelae of ocular surgical trauma. Preoperative indomethacin and preoperative meclofenamate are capable of attenuating postoperative pain following fallopian tubal ligation.[32, 106] Preoperative diclofenac is effective in decreasing postoperative pain following oral surgery,[235] but apparently less effective in prophylaxis for post-laparotomy pain.[232] Schultze and associates reported favorably on the preoperative administration of indomethacin, combined with epidural bupivacaine and morphine, in patients undergoing cholecystectomy.[211]

Adverse Effects

A word of caution is appropriate here if one is considering routine presurgical medication with nonsteroidal anti-inflammatory agents. Most of these compounds exert adverse effects on platelet function and may interfere with hemostasis. Inflammatory responses, although productive of undesirable effects (pain, edema, functional impairment), are nevertheless immune responses, and presumably protective. Prostaglandins may be quite necessary for normal wound healing,[135] and prostaglandin inhibitors may potentially mask the febrile response to infection, which is an important monitor of postoperative infection. Prostaglandins are intimately involved in the regulation of kidney function; their inhibition may lead to a variety of undesirable effects, which are well reviewed by Carmichael and Shankel[37] and include sodium and water retention, hyperkalemia, elevation in blood pressure, and impaired response to diuretics. Analgesic nephropathy is the condition of renal impairment and failure associated with interstitial nephritis or renal papillary necrosis occasionally seen following the administration of these compounds. In view of the potential adverse consequences of these medications, care must be taken in their perioperative use, and renal and circulatory parameters should probably be monitored postoperatively.

Clinical Use

As analgesic compounds, nonsteroidal anti-inflammatory agents are extensively applied in situations involving musculoskeletal pain and post-traumatic and inflammatory pain, in view of the previous discussion. It should be pointed out that there are additional situations in which prostaglandin activity may play a direct role in the pathogenesis of pain, such as in dysmenorrhea, renal colic, and biliary colic, which are forms of visceral pain. Prostaglandins appear to be involved in the mechanism of contraction of smooth muscle,[207] including uterine smooth muscle, and dysmenorrhea has long been managed with prostaglandin-inhibiting medication.[55] In the kidney, prostaglandins may increase pressure within the renal pelvis in the patient with ureteral obstruction, and the prostaglandin inhibitor diclofenac was reported to be more effective in treating ureteric colic than morphine.[136] Diclofenac was likewise evaluated favorably in the management of biliary colic.[33]

Although most nonsteroidal anti-inflammatory analgesics are available only in oral or rectal form, these routes of administration are not always possible or desirable. It is of interest that there are medications of this class that are available or are becoming available in parenteral form. A number of these have been evaluated in the situation of postoperative pain management and include dipyrone,[126] lysine acetylsalicylate,[125, 228] indomethacin,[146] indoprofen,[192] suprofen,[200] diclofenac,[232] and ketorolac.[91, 172] The increasing availability of such parenteral preparations further increases the therapeutic options for the clinician in the management of acute pain.

NEURAL BLOCKADE

Regional anesthetic techniques for the management of acute pain involve the intermittent or continuous administration of local anesthetic agents in order to interrupt sensory transmission. Most nerve block techniques are not pain specific. Noxious as well as non-noxious stimuli are blocked alike; sympathetic activity and, more often than not, a certain amount of motor activity is blocked as well. This discussion examines the various modalities of neural blockade available to the clinician and some of the issues regarding their appropriate application. A detailed discussion of the use of epidural and intrathecal analgesic techniques, particularly with regard to opioids and opioid/local anesthetic combinations, is presented in the article by Gregg in this issue and will not be replicated here.

The use of a local anesthetic nerve block requires that the duration of action of the anesthetic exceed the duration of the painful stimulus it is intended to block; this is, it is hoped, the case when local anesthetics are used to block surgical stimuli. Some degree of post-surgical analgesia will be possible if there is residual sensory block at the end of the procedure. Additionally, the block may be administered at the end of the procedure solely for the purpose of postoperative analgesia; for example, following a general anesthetic. Such single injection techniques may be appropriate in the setting of outpatient surgery, and usually when the extent of surgical trauma is fairly minimal. In the hospitalized patient who has undergone a more extensive surgical procedure, continuous regional techniques (whereas local anesthetics are repeatedly dosed or continuously infused via catheter) may be more appropriate.

Melzack and associates have reported that in most cases pain is negligible by the fourth postoperative day, but that a substantial portion of the post-surgical population (31 per cent) will have pain beyond the fourth day.[147] This is perhaps the population for whom, because of concern of increased risk of perioperative morbidity, continuous regional analgesia might be appropriately used and for whom the single postoperative nerve block or multiple repeated nerve blocks may be inappropriate, impractical, or undesirable. There is evidence to indicate that continuous epidural analgesia, for example, provides superior pain control when compared with conventional narcotic regimens[143, 186] and may significantly lower the incidence of postoperative morbidity in some cases.[251] It has been reported that continuous neural blockade performed in the perioperative period prior to and during amputation may provide "prophylaxis" against the development of postamputation deafferentation (phantom limb) pain, an additional benefit of this mode of acute pain control.[9] The sympathectomy provided by continuous epidural blockade may provide a desirable degree of vasodilation postoperatively following peripheral vascular procedures or plastic surgical grafting procedures.

Continuous epidural analgesia can be an excellent and versatile means of managing acute pain. The clinician must be prepared, however, to deal with a number of issues that arise as a consequence of the nature of epidural blockade. Continuous monitoring must be provided with regard to sympathectomy and circulatory function, CNS toxicity, unduly high levels of segmental blockade, and protection of anesthetized body parts not adequately under control of the patient. Ambulation may be delayed, and urinary catheter is often necessary because of impaired micturition. The benefits should, of course, outweigh the risks of continuous epidural analgesia and costs of the escalated level of clinical care mandated by the technique.

Local Anesthetic Wound Perfusion

In addition to continuous epidural anesthesia, alternative continuous catheter techniques have been described and are receiving increasing attention for providing continuous analgesia in a variety of settings (Table 2). More than 30 years ago, a technique of inserting an indwelling catheter beneath the anterior rectus sheath for the purpose of continuous postoperative abdominal wound perfusion with local anesthetic was described;[88] this method of controlling incisional pain was reported to have significant advantages over continuous epidural analgesia for post-laparotomy pain in a later comparative evaluation of the technique.[206] Of course, the avoidance of sympathectomy, urinary retention, and preservation of ambulation would be reasons to prefer such a technique over epidural blockade. Levack and associates also reported favorably on the perfusion of subcostal incisional drains with bupivacaine for analgesia following splenec-

Table 2. *Currently Available Continuous Regional Anesthetic Techniques by Body Region*

BODY REGION	CONTINUOUS REGIONAL ANESTHETIC TECHNIQUE
Head/neck	—
Upper extremity	Brachial plexus catheter
Chest wall/upper abdomen	Thoracic epidural catheter, intercostal catheter, interpleural catheter
Lower abdomen/pelvis/perineum	Rectus sheath catheter, lumbar epidural catheter
Lower extremity	Lumbar epidural catheter, lumbar plexus catheter, sciatic perineural catheter

tomy and cholecystectomy and noted improvement in forced vital capacity and narcotic requirements.[130]

Continuous Brachial Plexus Anesthesia

A particularly versatile technique for providing upper extremity anesthesia and analgesia is that of brachial plexus cannulation for continuous local anesthetic infusion. Continuous brachial plexus anesthesia was initially described by Ansbro in 1946,[5] using an indwelling needle fixed to the patient by means of a cork and adhesive tape. The use of the modern indwelling plastic catheter for brachial plexus cannulation was introduced by DeKrey some 20 years later.[56] Since that time, a number of approaches to brachial plexus cannulation have been described, including the axillary approach,[212] the supraclavicular approach,[100, 198] and the infraclavicular approach.[184] Figure 1 depicts two commercially available catheters designed for brachial plexus cannulation. Each of these techniques is based on the concept of perivascular injection[245] into the fascial sheath containing the neurovascular bundle that comprises the brachial plexus. Although the concept of compartmentalization of the brachial plexus components[230] has generated some controversy with regard to single as opposed to multiple injections (multiple injections supposedly being necessary to ensure that all brachial plexus components are blocked within their respective compartments), it has been known for years that single-compartment injections such as the transarterial technique *do* in fact produce satisfactory anesthesia with 90 per cent and greater success rates in the hands of some. Selander has discussed this controversy and in his review concludes that the fibrous septae that define these compartments do not pose a significant barrier to the spread of local anesthetics.[213]

Continuous Regional Analgesia for the Lower Extremities

Continuous lower extremity analgesia is typically provided by continuous lumbar epidural anesthetic techniques; this is necessarily accompanied by the undesired side effects of epidural anesthesia, which have been mentioned previously. Alternatives to epidural anesthesia for providing continuous lower extremity analgesia have been described, however, that could potentially eliminate one or more of the undesired consequences of epidural blockade listed.

Continuous femoral analgesia administered by indwelling inguinal catheter has been reported as a successful technique for management of post-surgical lower extremity pain.[197] The approach used by Rosenblatt was based on Winnie's inguinal perivascular technique of introducing local anesthetic into the lumbar plexus.[246] Alternatively, Parkinson and Mueller have examined the paravertebral approach to the lumbar plexus,[181] based on the "psoas compartment block" concept,[41] as a means of introducing a catheter for continuous lower extremity anesthesia/sympathectomy and have reported this approach to be capable of producing more complete anesthesia, particularly of the obturator and iliopsoas nerves, which they found were

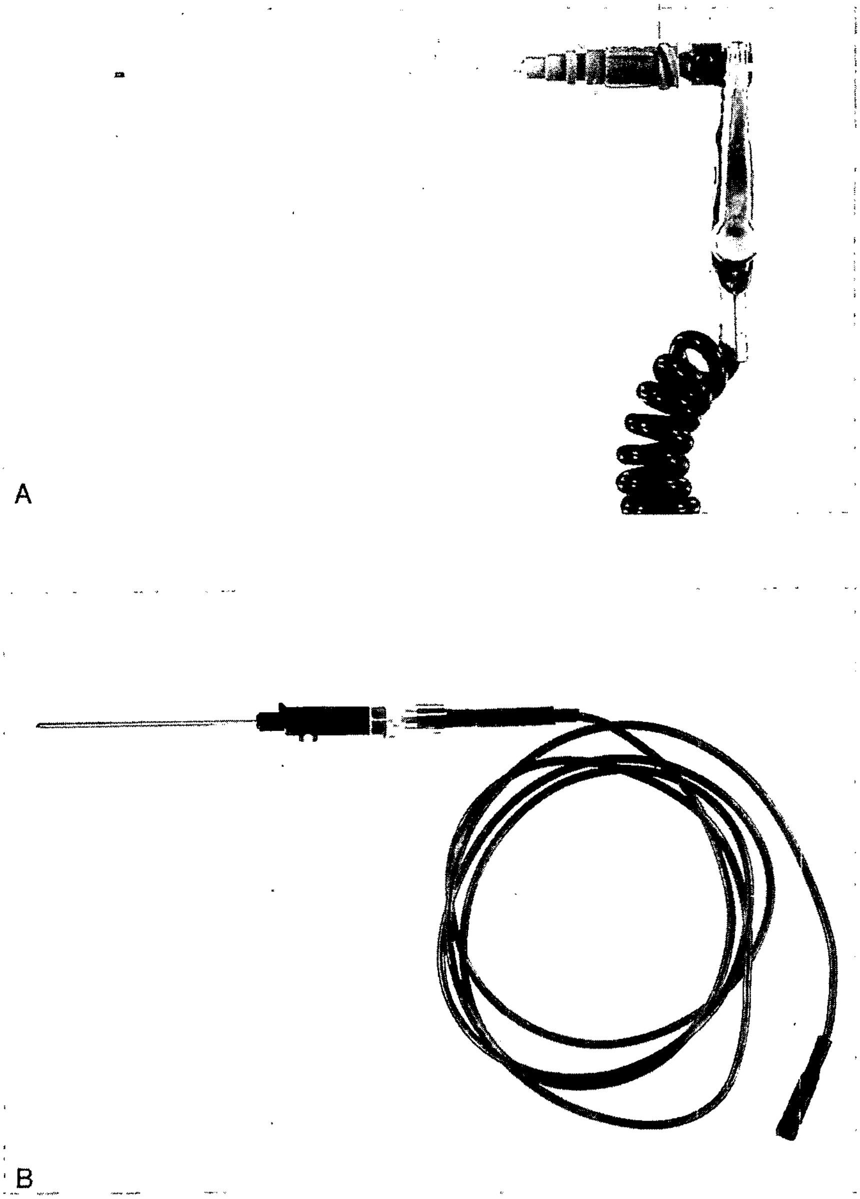

Figure 1. Two commercially available catheters are depicted in the photographs; the brachial plexus anesthesia catheter (Arrow International, Inc., Reading, PA; *A*) and the Contiplex brachial plexus catheter (Burron Medical Inc., Bethlehem, PA; *B*). Both are shown with stimulator leads attached. Photographs by permission of the manufacturers.

incompletely blocked by the inguinal perivascular approach. In order to complete the sensory block of the lower extremity, Smith and associates combined a continuous inguinal perivascular block with a continuous sciatic perineural block for preoperative sympathectomy and analgesia, surgical anesthesia, and postoperative analgesia in a patient with a gangrenous foot.[220] The advantages of these techniques over continuous lumbar epidural anesthesia are the avoidance of bilateral sensorimotor block and bilateral sympathectomy; this should certainly appeal to any clinician who has had the experience of managing continuous epidural infusions on a surgical ward.

Intercostal Neural Blockade

Continuous epidural analgesia provides excellent lower abdominal, pelvic, and perineal analgesia. However, the upper abdomen and thoracic wall may lend themselves to alternative regional techniques. The intercostal nerve block, a long-standing technique for anesthetizing the chest wall and upper abdomen,[15] was recognized quite early as a means of minimizing the effect of pain on postoperative respiratory function, the consequence of which is splinting, hypoventilation, and atelectasis.[92] Regardless of the hypothetical advantages of this block, a number of investigators have found it difficult to document improvement in repiratory parameters in post-surgical patients receiving intercostal blocks[71, 72, 87] or any measurable advantage over narcotic therapy.[71] Moreover, respiratory failure following intercostal nerve blocks has been reported,[38, 52] presumably owing to motor block and loss of chest-wall-assisted breathing in the patient with pre-existing respiratory impairment. Additionally, complications such as pneumothorax, hypotension,[218] and total spinal anesthesia[20] are possible.

There are alternatives to performing multiple intercostal nerve blocks: continuous catheter techniques for intercostal anesthesia have been described.[1, 173] The obvious advantage is the ability to provide prolonged analgesia without the inconvenience of multiple, repeated needle sticks and their attendant risks. Continuous intercostal anesthesia via indwelling catheter has been reported to be efficacious in the management of post-traumatic chest wall pain,[137, 173] and post-surgical analgesia following biliary and kidney procedures.[157, 158] A large volume of local anesthetic (20 ml) administered through the intercostal catheter may result in spread of anesthesia well beyond the cannulated dermatome and even to the contralateral side,[148] and this is felt to represent prevertebral[123] and possibly epidural spread of local anesthetic.

Continuous Interpleural Analgesia

The most recent development in continuous regional anesthetic techniques has been the introduction of the concept of interpleural analgesia by Kvalheim and Reiestad in 1984.[124] Also referred to as intrapleural anesthesia by many investigators, the technique involves insertion of a catheter between the visceral pleura and parietal pleura and deposition of 10- to 30-ml doses of local anesthetic. Radiographic spread of 20-ml injection volumes extends from diaphragm to apex,[29] and hence the possible involvement of multiple neural structures including the intercostal nerves, and paravertebral thoracic sympathetic chain, the splanchnic nerves, and the phrenic nerve is conceivable. A 30-ml dose of 0.5 per cent bupivacaine is capable of producing unilateral pinprick anesthesia over as many as 8 dermatomes,[214] from T4 to T11 in one patient. Rocco and coworkers reported that a 0.5 per cent bupivacaine concentration, but not a 0.25 per cent concentration, produced pinprick anesthesia, and that the former but not the latter correlated with good analgesia for rib fractures,[195] suggesting that analgesia in this situation depends on anesthetizing the intercostal nerves. On the other hand, relief of pancreatic pain by the interpleural technique may involve anesthesia of the splanchnic nerves or the thoracic sympathetic chain.[66] Intermittent and continuous infusion techniques have been described, as a means of providing satisfactory analgesia for post-surgical pain following mastectomy and cholecystectomy;[29, 34, 189, 214] additionally, this analgesic technique seems quite suited for the thoracic trauma patient with multiple rib fractures.[195] Unfortunately, post-thoracotomy analgesia provided by this technique does not appear to approach the level of satisfaction seen in the other previously mentioned situations.[69, 196]

Most investigators have used the technique described by Kvalheim and Reiestad for cannulation of the intercostal perineural space using a Tuohy needle and an epidural catheter,[124] or having the catheter positioned intrathoracically by the surgeon operating within the thoracic cavity. An alternative is to utilize indwelling chest drainage tubes for instillation of local anesthetic, a technique that requires clamping the chest tube for 15 to 20 minutes, provided that the patient is able to tolerate this.[128] Reported complications of interpleural catheter insertion and dosing include pneumothorax and seizures resulting from intravascular injection,[29, 214] although the overall incidence of complications appears to be low.

Other Local Anesthetic Techniques

Although this section has primarily discussed continuous regional techniques, the benefits of single-injection regional blocks for post-surgical analgesia in situations of relatively minor and outpatient surgery should not be diminished. Inguinal, iliohypogastric, and penile dorsal nerve blocks, as well as caudal blocks and topical anesthetic agents are all effective as "single block" techniques in a variety of outpatient pediatric surgical procedures.[30, 58, 188, 216, 233] Topical anesthetics applied to mucosal surfaces following operative trauma, for example, tonsillectomy, can provide very satisfactory analgesia.[262] Wound infiltration is probably the simplest technique for providing wound analgesia but is all too frequently neglected. In the case of episiotomy infiltration, even saline was noted to be effective in reducing post-episiotomy pain,[117] presumably because of the mechanical pressure effect of the infusate on edema formation within the wound. Pain following tubal ligation, because of ischemia and spasm within traumatized tubal tissue, is quite effectively attenuated by spraying or infiltrating the mesosalpinx with local anesthetic, and this can be performed through the laparoscope.[35, 231]

Local anesthetic techniques are clearly among the most effective and versatile means for providing relief of acute pain. Many of these techniques have existed for years. Even the clinician who knows only one or two of these techniques may be able to benefit a great number of patients.

CRYOANALGESIA

The relatively limited duration of our presently available local anesthetics with regard to the chronicity of certain pain syndromes, particularly in situations where continuous regional anesthetic techniques are not appropriate, has spurred interest in application of neurodestructive techniques for the management of pain. Such an approach to sensory interruption is generally within the domain of the management of chronic pain syndromes, although nerve lesion techniques have been considered in certain limited situations of acute pain management, such as the treatment of post-thoracotomy pain. The cryolesion has found favor with some investigators because of theoretical advantages over other nerve lesion techniques.

Chemical neurolysis and surgical sectioning of nerves are generally reserved for the terminal cancer patient whose life expectancy is limited to months. A number of reasons have steered clinical practice in this direction: chemical agents such as phenol have a duration of effectiveness of only 2 to 4 months, and return of sensation is often accompanied by painful neuritis. Nerve lesion techniques such as surgical sectioning may additionally be accompanied by the formation of painful neuromas, deafferentation pain, sympathetically maintained pain syndromes, and anesthesia dolorosa. The popularity of chemical and surgical peripheral nerve lesion techniques has largely waned in the treatment of nonmalignant chronic pain syndromes.[247]

On the other hand, cryolesioning produces a second degree nerve injury, or axonotmesis, at temperatures of −20 degrees Celsius and lower.[226] The surrounding architecture of the peripheral nerve and its wrappings is preserved, and hence the nerve heals without the scarring seen following other nerve lesions. Hence, temporary analgesia, lasting from weeks to months, is the result of the cryolesion. The technique of cryoanalgesia, described over a decade ago,[134] involves placement of a cryoprobe, the tip of which is chilled to temperatures of −60 degrees Celsius and lower by refrigerants such as nitrous oxide or liquid nitrogen, at the appropriate peripheral nerve site in order to produce a cryolesion. The lesion is best guaranteed by surrounding the nerve with the resultant ice ball under direct vision, although "blind" percutaneous techniques have been described.[28]

As a method of managing chronic pain, cryoanalgesia has been utilized in the management of facial pain syndromes[21] and zygoapophyseal joint pain;[28] the need to repeat such a procedure every few months may make the technique less desirable in some patients. As a method of managing acute pain, the use of the cryoprobe has been most frequently used for intercostal nerve cryolysis for post-thoracotomy pain. The initial clinical reports were quite favorable with regard to satisfactory post-thoracotomy analgesia,[93, 141] although improvement in pulmonary function was difficult to demonstrate.[115] Orr and associates showed similar results in patients receiving intercostal cryolysis and in those receiving morphine infusions after thoracotomy.[175] Subsequent reports have been quite guarded in their enthusiasm with regard to measurable advantages of intercostal cryolysis.[35, 201] Analgesia is often incomplete, with residual discomfort at chest tube sites, midback, and the shoulder, often requiring supplementary narcotic medication.[35, 193] Problems such as unwanted postoperative nipple anesthesia,[193] chest wall bleeding,[201] potential cryogenic damage to surrounding tissues, including full-thickness skin destruction,[185] and post-procedural intercostal neuralgias[193, 201] have been described, although these may not be very common occurrences. Cryoanesthesia equipment is rather costly, and a stronger endorsement of the efficacy, utility, and versatility of this particular modality may be required for many clinicians before investing in such a device.

MISCELLANEOUS TECHNIQUES

The preceding sections probably only scratch the surface of the vast and ever-growing possibilities of pharmacologic intervention in pain perception. The following section will cite additional ventures into this bold new pharmacologic world, spawned by scientific advances in the understanding of neurophysiochemical mechanisms of pain. It should be emphasized that broad clinical experience is definitely lacking in the following modalities to be discussed. The intention here is to merely stimulate and to inspire an appreciation in the new directions being explored in the medical management of acute pain.

Intrathecal and Epidural Ketamine

The spinal administration of ketamine has been examined by a number of investigators as an alternative to spinal local anesthetics and opiates, which are imperfect agents by virtue of their unwanted side effects (undesired sympathetic and motor block, respiratory depression, and so forth). It should be pointed out, however, that ketamine does in fact possess local anesthetic properties. Dowdy and coworkers,[61] evaluating the local anesthetic effects of ketamine, found it to be equimolar in potency with procaine with regard to blocking frog sciatic nerve action potentials, and that it was quite capable of producing reversible motor block when injected intrathecally into dogs. Spinal ketamine also produced reversible sensorimotor block in sheep and monkeys.[238] Bion, using intrathecal ketamine as a surgical anesthetic in Cambodian battle-victims, found 50-mg subarachnoid doses of ketamine to be capable of producing motor loss and sensory anesthesia as high as the T2 dermatome, and described hypotension in one patient.[23] In addition to the local anesthetic effects seen at the higher doses mentioned here, there is evidence of spinal analgesia at lower doses without overt neural blockade; this analgesia may be naloxone-reversible,[3] but this is disputed by Tung and Yaksh,[234] who instead found this analgesia to be reversible by methysergide but not by naloxone, suggesting a serotonergic and not an opioid mechanism of action. The contribution of supraspinal effects on spinal ketamine analgesia is presently unclear.[156]

Mankowitz and coworkers administered relatively small epidural doses of ketamine (4 mg) and reported the production of analgesia in cancer patients apparently without evidence of local anesthetic block.[142] Despite their initial success, this same group reported a year later that doses as high as 50 mg did not produce satisfactory postoperative analgesia.[203] Other clinical evaluations have been published since then, with varying results.[108, 116, 151, 159] Kawana and coworkers concluded that doses of up to 8 mg simply did not provide adequate analgesia following abdominal gynecologic procedures;[116] Mok and associates reported that 15 mg of epidural ketamine provided an average of only 3.8 hours of analgesia and were reluctant to increase the dosage because 10 per cent of their patients showed evidence of psychotomimetic effects.[151]

Other Novel Spinal Analgesic Agents

Of additional interest here are the reported analgesic effects of epidural and intrathecal clonidine in animals and in man,[47, 68, 229, 250] felt to involve spinal adrenergic mechanisms of analgesia. Intrathecal baclofen produces analgesia in the monkey[250] and given systemically in man prolongs epidural fentanyl analgesia;[178] baclofen is felt to inhibit dorsal horn transmission of nociception by a GABA-agonist effect. Both systemic[118] and epidural droperidol[10] appear to potentiate the effect of epidural opiates, and this may involve a spinal dopaminergic mechanism. Intrathecal calcitonin is productive of analgesia in the setting of cancer pain as well as experimentally induced pain[82] and postoperative pain;[149] the mechanism for calcitonin analgesia is unclear.

The evaluation of new spinal and epidural agents should be done in a rational way, lest the clinical investigator be accused of wanting to put anything and everything into the epidural space. Animal studies should not only show the production of measurable analgesia, but also provide some satisfactory understanding with regard to mechanism of action; for example, are spinal receptors for the substance present, and if not, might these same effects be mediated by systemic absorption as well? Receptor antagonists should, of course, reverse the analgesia if a receptor mechanism is felt to be operant. Detailed toxicologic studies of the spinal cord, as well as effects on spinal blood flow should probably be examined. Simply because a compound is an "endogenous substance" in no way guarantees its safety on spinal administration. For example, Stephens and coworkers found that intrathecally administered dynorphin, an endogenous peptide, produced flaccid motor paralysis in rats, suggesting possible ventral horn toxicity.[224] Of course, the neurotoxicity of preservatives and solvent (vehicle) should be examined carefully in any drug preparation.

Novel Systemic Analgesic Agents

Anticholinesterase agents have been evaluated as analgesics in light of a growing awareness of cholinergic mechanisms of analgesia. At the spinal level, it is observed that intrathecal physostigmine potentiates spinal opiate analgesia whereas intrathecal atropine diminishes spinal opiate analgesia in rats.[59] Intravenous physostigmine appears to produce analgesia in chronic pain states[210] as well as in postoperative pain.[182]

Tricyclic antidepressant medications and anticonvulsant medications have been employed in chronic pain disorders,[89, 227] although little evaluation of such agents in the setting of acute pain has been done. Tricyclic antidepressants, by inhibiting neuronal re-uptake of serotonin and norepinephrine, appear to activate pain modulatory systems subserved by these monoamines. Injected intrathecally, amitriptyline potentiates morphine analgesia in the rat.[27] McQuay and associates recently evaluated fluradoline, a tricyclic compound, in the treatment of postoperative pain.[140]

Anticonvulsant compounds are efficacious in a variety of neuropathic pain syndromes such as trigeminal neuralgia; they are felt to attenuate spontaneous neuronal discharges by virtue of their membrane-stabilizing effects,[227] and possibly produce analgesia by an effect on GABA metabolism;[103] phenytoin and carbamazepine are commonly used in this context. Richards and associated reported favorably on the analgesic effects of trimethadione, an anticonvulsant compound used primarily for petit mal epilepsy.[191] This group found trimethadione effective in lowering the intensity of experimentally induced pain, headache, dysmenorrhea, and postoperative pain. Their report was published in 1946.

SUMMARY

The possible options for the management of acute pain are quite numerous and continue to expand as our understanding of the mechanisms of pain becomes increasingly sophisticated. Many of the options discussed have been available for years, and their present underutilization may be a reflection of the lack of emphasis on the importance of management of acute pain. An illustration of this would be our present ritual of prescribing narcotics postoperatively, a longstanding, but unfortunately inadequate practice. Because of poor selection and scheduling of doses, postoperative analgesia is typically a less than satisfactory experience for many patients convalescing in a hospital following surgery.

The clinician should of course be guided by the clinical situation itself in order to determine what modality or combination of modalities may be appropriate for pain management. Certain techniques, such as continuous local anesthetic infusions, may warrant an escalated level of monitoring and ancillary care. Other techniques, such as the infiltration of a wound with local anesthetic or the addition of a nonsteroidal anti-inflammatory agent to a regimen of mild oral narcotics are so simple that excluding them from patient care is almost callous and inconsiderate. Attention to the mechanisms of pain that may be present in a given situation, whether it be muscle spasm, ischemia, inflammation, edema, or nerve injury, may guide the clinician toward a more rational approach in managing that pain.

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Analgesia for Post-Cesarean Delivery Pain

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The past 20 years have seen a dramatic increase in the cesarean birth rate. In the late 1970s the cesarean section rate was less than 6 per cent. Today rates of 15 to 20 per cent are considered the norm. In many high-risk centers, rates of 25 per cent or higher are common. Many reasons have contributed to the increased cesarean section rate. The widespread use of fetal heart rate monitoring has made it easier to identify infants at potential risk of ischemic injury during the stresses of labor and delivery. It is a commonly held belief that serious trauma to the newborn can be reduced by avoiding potentially difficult vaginal deliveries. Additionally, the current crisis in obstetric malpractice lawsuits involving cases of poor neonatal outcome has probably contributed to the low threshold among many obstetricians for advising cesarean delivery. The rapidly declining perinatal mortality rate has been, in part, attributed to the increased cesarean delivery rate. Whatever the reasons for the increased cesarean delivery rate, approximately one in five newborns in the United States will be delivered by cesarean section.

A number of important factors have been identified that influence the occurrence, intensity, quality, and duration of postoperative pain.[5] These include (1) the physiologic and psychologic makeup of the patient; (2) the preoperative psychologic, physical, and pharmacologic preparation of the patient; (3) the operation itself—site, nature, duration, type of incision, intraoperative trauma; (4) presence of serious postoperative complications; (5) the anesthetic management before, during, and after the operation; and (6) the quality of postoperative care. The identification of these factors has helped us to modify our practices so as to optimize patient care and reduce postoperative pain.

Obstetric anesthesia practice has been modified to make the cesarean section experience as comfortable and natural for the parturient

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as possible. As a result, many institutions are moving away from employing general anesthesia for cesarean sections except in the most emergent situations. Spinal or epidural anesthesia allows the patient to be awake for the delivery and in most cases to interact with her newborn even before surgery is completed. Many hospitals allow or even encourage the presence of a support person during a cesarean delivery under regional anesthesia.

Most women undergoing cesarean delivery are not physically ill, do not view themselves as sick, and have no wish to suffer pain or an uncomfortable convalescent period. These patients wish to have normal interactions with their newborns without the distractions of postoperative pain or side effects from medications. Any method of pain control that can make the recovery period comfortable and minimally disabling has significant impact for these patients. Optimal analgesic management should be effective, safe for both mother and newborn, and minimally intrusive to deliver. Recent developments in postoperative pain management have resulted in techniques that have particular advantages for the patient who has undergone cesarean section. This article reviews some of these developments, with particular focus on the use of intraspinal narcotics and patient-controlled analgesia (PCA).

CONVENTIONAL POST-CESAREAN ANALGESIC MANAGEMENT

Traditional management of post-cesarean pain has been with either intravenous (IV) or intramuscular (IM) injections of various narcotic agents. Intravenous injections are effective in rapidly achieving adequate analgesic blood levels of the drug but have the disadvantage of the rapid appearance of side effects such as sedation and respiratory depression and of short duration of action as the drug is redistributed. For this reason, IV injections of analgesics are usually reserved for the recovery room where both close nursing supervision is present and repeated injections may be given when necessary.

The most common method of managing pain following cesarean section has been the use of IM narcotics prescribed on a time contingent, as needed basis. The inadequacies of this mode of pain management have long been recognized.[43, 62] These studies indicated that 75 per cent of patients reported that they remained in significant pain during their postoperative period. House officers prescribed narcotics in amounts that were approximately 50 to 65 per cent of what had been established as effective doses; and nurses administered approximately 40 to 50 per cent of the inadequate amounts of medication prescribed.

Wide variation in patient requirements for analgesics sometimes leads to overmedication but much more commonly to under-treatment when "routine" postoperative pain medication orders are written. Patients may have blood levels of narcotic higher than is necessary for analgesia soon after intramuscular injection, resulting in sedation or other side effects, and may have inadequate blood levels of the drug before the next injection can be given. In addition, the IM route is traumatic and distressing to some patients. Patients frequently seem to complain of excessive delays from the time of request for pain medication until the nurse is able to respond and administer the ordered injection.

A retrospective review of over 100 patients at our institution who underwent cesarean delivery with a regional anesthetic and subsequently were treated with IM narcotics showed that a mean dose of 91 mg of narcotic (expressed as morphine equivalents) were administered IM for postoperative analgesia.[56] Assuming a 10-mg dose per injection this would indicate that an average of about nine injections were given per patient.

Recently, the use of parenteral mixed agonist/antagonist opioids has been advocated by the manufacturers of these agents. Drugs such as butorphanol (2 mg), nalbuphine (10 mg), and buprenorphine (0.3 mg) have been reported to have good analgesic properties, and some demonstrate a ceiling effect with regard to respiratory depression. These drugs, however, all have some respiratory depressant properties and may also have a ceiling effect for analgesia.[58] A notable side effect of these opioids is sedation that is considerably greater than that seen with equianalgesic doses of morphine. For these reasons and because there has been little clinical experience with these drugs in the obstetric population, they have not gained widespread popularity.

INTRASPINAL NARCOTIC TECHNIQUES

The history of intraspinal narcotic administration for analgesia is relatively short; however, it is interesting that obstetric anesthesia was one of the first areas where this new modality was utilized. Yaksh and Rudy in 1976 first described the analgesic properties of morphine when injected into the subarachnoid space in rats.[68] In 1979 Wang et al reported on the efficacy and safety of morphine 0.5 to 1.0 mg injected subarachnoid in patients suffering chronic cancer pain.[63] Also in 1979, Behar et al first described the use of epidural morphine in the treatment of pain.[4] That same year Wolfe and Nicholas communicated their experience in treating post-cesarean pain with the use of fentanyl, 100 μg, given epidurally.[66] Since these early reports, numerous studies have demonstrated the efficacy, duration, and side effects of a variety of narcotic agents administered via a spinal route for the treatment of post-cesarean pain.

The techniques that employ intraspinal narcotics for post-cesarean analgesia are intended to deliver the drug at opioid receptors in the spinal cord that are involved in pain transmission. Opioid receptors can be found in spinal cord laminae (substantia gelatinosa, Rexed's laminae, I,II,V), spinal cord nuclei, as well as other neural and non-neural tissues. At least five different opioid receptors have

Table 1. *Opioid Receptors*

RECEPTOR	RESPONSE
Mu	Analgesia, miosis, respiratory depression
Kappa	Sedation
Sigma	Tachycardia, tachypnea, hypertonia
Delta	Analgesia (?)
Epsilon	?

been identified (Table 1), which may subserve several functions in addition to modulating pain perception. Clinically, the goal of epidural and intrathecal administration of narcotics is to attempt to deliver the drug to selected receptors sites in the spinal cord in order to produce analgesia. The alternative is to administer systemic narcotics that activate multiple receptors throughout the central nervous system, resulting in a number of effects in addition to analgesia.

Epidural Narcotic Analgesia

A number of studies published in the early 1980s provided convincing evidence of the efficacy of epidural morphine for providing post-cesarean pain relief. Many of these studies used a randomized, double-blinded, placebo-controlled design.[10, 14, 18] Epidural morphine in doses of 4 to 8 mg resulted in significantly better pain relief, lower parenteral narcotic requirements, and longer analgesic duration than did placebo. In two of these studies the mean duration of pain relief was in the range of 22 to 27 hours.

Although it is not particularly surprising that epidural morphine would provide better pain relief than placebo, more convincing evidence of the superiority of this route of analgesic administration has emerged from studies comparing epidural narcotic analgesia with more traditional methods of postoperative pain control such as IM and IV narcotic administration. Rosen et al[54] demonstrated that a 2-mg dose of epidural morphine was ineffective in producing pain relief; however, epidural morphine in doses of 5 or 7.5 mg produced excellent analgesia that lasted 24 to 29 hours. In comparison, 7.5 mg of IM morphine produced moderate analgesia with a duration of approximately 3 hours (Fig. 1). In a randomized double-blinded study, Cohen and Woods compared the efficacy and side effects of morphine, 5 mg, given either by IV or epidural injection in post-cesarean patients.[17] Those patients given epidural morphine reported significantly better analgesia that lasted longer and required less supplemental analgesic administration. The mean duration of analgesia in the epidural group was 16.1 hours compared with 4.4 hours in the IV group. In addition to longer and better analgesia, patients receiving epidural morphine were noted to ambulate almost 6 hours earlier than those in the IV group.

Plasma levels of morphine following epidural injection are found

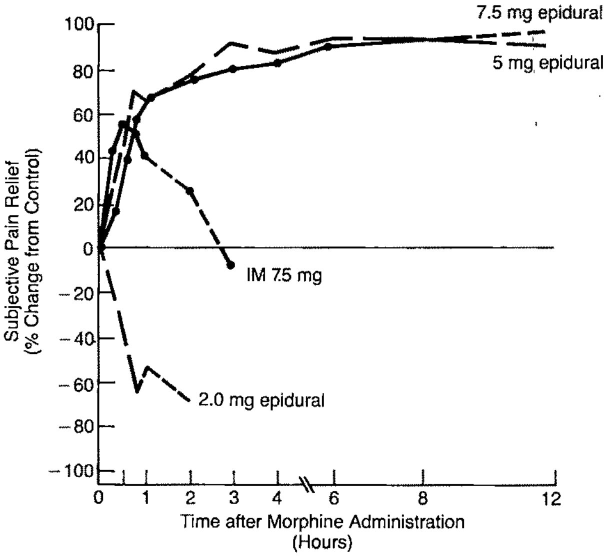

Figure 1. Per cent changes in pain relief (from control) for 40 patients after intramuscular (7.5 mg) or epidural (2mg, 5 mg, or 7.5 mg) administration of morphine after cesarean delivery. (*From* Rosen MA, Hughes SC, Shnider SM, et al: Epidural morphine for the relief of postoperative pain after cesarean delivery. Anesth Analg 62:666, 1983; with permission.)

to be generally similar to those following IM injection.[19, 64] The analgesic onset, however, usually does not occur until 30 minutes to 1 hour following injection. For this reason it is important to administer the morphine as soon as possible so that the analgesic onset will occur prior to the complete regression of local anesthetic block. Analgesia seen with IV or IM administration of morphine parallels the serum levels of the drug.[9] Following epidural administration of morphine, the analgesic effect persists long after the serum drug concentration has decreased.[64] This observation in addition to the much closer correlation of CSF drug concentrations with analgesic effect have provided some of the evidence that epidurally administered narcotics act by entering the spinal cord and exerting their effect locally.

Morphine is probably the most commonly used epidural narcotic for providing postoperative pain relief. However, since Wolfe and Nicholas first reported the use of epidural fentanyl in post-cesarean patients, it also has been popular in the obstetric population. Because fentanyl has a relatively high lipid solubility it has been postulated that it should have a rapid onset and perhaps a lower likelihood of respiratory depression because most of the drug would rapidly bind to spinal cord tissue leaving little in the CSF to migrate to higher respiratory centers.[12] Naulty et al reported that fentanyl, 50 μg, produced analgesia in about 7 minutes that lasted approximately 4.5 hours.[44] This dose was found to be the minimally effective dose.

Larger doses did not produce better quality or longer-lasting analgesia. In another study investigating the use of epidural fentanyl in post-cesarean patients it was found that the addition of epinephrine to the drug produced a modest prolongation in analgesic effect although the incidence of pruritus was also increased from 17 to 44 per cent.[53] Thus, fentanyl has been shown to produce adequate post-cesarean analgesia with minimal side effects, although it has the disadvantage of a short duration.

Reports of other opioids given epidurally for post-cesarean pain relief have appeared in the literature; however, it does not appear that these agents are in widespread use in the United States. Brownridge and Frewin demonstrated that meperidine, 50 mg, given epidurally provided significantly better pain relief than either placebo or meperidine, 100 mg, given IM.[13] Although analgesia and patient satisfaction were greater with the epidural meperidine than with IM meperidine, the duration of analgesia was no different, averaging 2.5 to 3 hours. Methadone given epidurally has been shown to produce good post-cesarean pain relief. The mean duration of analgesia from first administration until the next dose was required was 6.9 hours.[25] In another study the effect of epidural hydromorphone was evaluated in post-cesarean patients.[16] Ninety-two per cent of patients given hydromorphone, 1.0 mg, reported good or excellent analgesia. The mean duration of analgesia was 13 hours. Although the study did not involve a direct comparison with epidural morphine, the authors concluded that the observed side effects, quality of analgesia, and duration were similar to that reported for morphine.

Compared with morphine, the high lipid solubility and potency of sufentanil suggest a potential benefit for use as an epidural narcotic analgesic. Several recent studies have addressed the issue of using epidural sufentanil for pain control following cesarean section.[40, 46, 59] These studies demonstrated that adequate analgesia could be obtained with a duration of between 200 and 400 minutes with epidural doses of sufentanil between 30 and 75 μg, respectively. Sufentanil has an onset of action in less than 5 minutes. The incidence of side effects were somewhat less than with epidural morphine; however, statistical significance was not reached, probably due to the small sample sizes. There is little advantage to adding epinephrine to the drug in an effort to increase its duration of action.[46] Epidural sufentanil appears to produce reliable post-cesarean analgesia with a slightly longer duration of action than fentanyl. However, of concern to the clinician using this drug is the potential of inadvertent IV injection of such a potent narcotic. In the doses required to produce adequate analgesia with epidural administration, one would expect significant respiratory depression.

The effects of epidural butorphanol have also been studied in the post-cesarean patient. Butorphanol is a drug which is a κ-agonist and μ-agonist/antagonist. It is believed that most morphine side effects, including respiratory depression, are μ-receptor mediated, and therefore a drug such as butorphanol may provide analgesia with minimal side effects. Naulty et al first reported the direct relationship between degree and duration of analgesia with epidural butorphanol in the dose range of 1 to 6 mg.[47] In another study, epidural butorphanol in doses up to 4 mg was compared with epidural morphine, 5 mg.[2] Compared with morphine, butorphanol demonstrated somewhat less analgesia, a more rapid onset, and a shorter duration (4 to 8 hours compared with 21 hours). No pruritus was seen in the butorphanol-treated patients but somnolence was noted.

Since the first reports of epidural narcotic administration for the control of pain, a number of side effects have been mentioned repeatedly. Some of these side effects such as pruritus, nausea and vomiting, or urinary retention can be troublesome or unpleasant. Other problems that have been reported, such as respiratory depression, constitute complications that are worrisome and potentially fatal.[12, 52, 63]

Among the side effects reported, pruritus is undoubtedly the one most frequently seen in post-cesarean patients treated with epidural morphine. The reported incidence varies widely, but is generally in the range of 60 to 90 per cent. Some evidence suggests that the obstetric patient may be more sensitive to both the analgesic properties as well as the side effects of epidural morphine. In one comparative study the incidence of pruritus was over twice as great in post-cesarean patients compared with patients undergoing other types of surgery.[67] Our own data in 193 patients given a mean dose of 4.3 mg epidural morphine indicates an incidence of 70 per cent. Forty-three per cent reported pruritus only on careful questioning and were not treated for this side effect. Twenty-two per cent were successfully managed with either diphenhydramine, 25 mg IM, or naloxone, 0.1 mg IV, although 6 per cent of our patients did not obtain satisfactory relief with this regimen.[15] Few studies have compared the side effects of various epidural opioids, although some reports would indicate that the incidence of pruritus may be less with more lipid soluble agents such as fentanyl or meperidine than with morphine.[13, 44, 53] Pruritus does not seem to be a side effect associated with epidural administration of the agonist/antagonist opioid butorphanol.[2]

The mechanism responsible for causing pruritus has not been elucidated. It appears to be a nonsegmental, highly variable phenomenon. Some evidence suggests that it is dose related, increasing in incidence as the concentration of narcotic in the cerebrospinal fluid increases. Pruritus associated with epidural opioid administration has been managed with modest success with parenteral antihistamines[15–17, 37, 54] even though there is no evidence that it is mediated by histamine release. Nalaxone administered in small doses, for example, 0.1 mg, or by continuous infusion seems to be more effective for the treatment of pruritus from this cause.[36, 37, 60] If the nalaxone is carefully titrated, it is usually possible to reverse pruritus without reversing the analgesic effect.

Nausea and vomiting are commonly encountered during pregnancy, following many operative procedures, and after a variety of anesthetic techniques. They are seen in post-cesarean patients given regional or general anesthetics. The reported incidence varies widely. Most studies have indicated a higher incidence of nausea and vomiting in patients treated with epidural morphine than in those treated with parenteral narcotics or non-narcotic analgesics. The mechanism of epidural narcotic-induced nausea and vomiting may involve direct stimulation of the chemoreceptor trigger zone (area postrema) of the medulla. Post-cesarean patients may be more prone to this side effect than nonobstetric patients.[67] Although the incidence of nausea has been reported to be as high as 53 per cent in the obstetric population following epidural morphine,[67] more commonly the reported incidence is in the range of 16 to 25 per cent.[15, 17, 37] In our experience 25 per cent of patients reported some degree of postoperative nausea on careful questioning, although only 11 per cent requested treatment for this side effect. Persistent nausea or vomiting after antiemetic therapy occurs in less than 2 per cent of our patients. The incidence of this side effect may be less following the use of more lipid soluble agents such as epidural fentanyl, meperidine, or agonist/antagonist agents such as butorphanol.[2, 13, 44, 47, 53] Treatment for nausea and vomiting associated with epidural narcotics has usually consisted of conservative doses of prochlorperazine (5 mg IM), droperidol (0.625 mg IV), or metoclopramide (5 to 10 mg IV). Two recent reports have indicated that transdermal scopolamine patches may be particularly effective in the treatment of nausea and vomiting associated with epidural narcotic administration.[38, 41]

Urinary retention is one of the recognized side effects associated with epidural narcotic administration. Voiding difficulties seem to be especially common following epidural narcotic administration in young male patients. The mechanism of urinary retention is still poorly understood, but is thought to be due to a direct sacral spinal action of the narcotic resulting in inhibition of the micturation reflex. Animal studies have demonstrated both a failure of the detrussor muscle to contract as well as failure of the external sphincter to relax in response to bladder filling.[23] Post-cesarean patients may have voiding problems for a number of reasons including trauma owing to labor or the operative delivery. Surprisingly, urinary retention has rarely been cited as a significant problem associated with epidural narcotic analgesia in the post-cesarean population. One of the reasons for this may be that it is common practice among many obstetricians to leave an indwelling urinary catheter in place for the first 12 to 24 hours following cesarean section. Although higher incidences of problems with voiding have been reported by others following epidural morphine,[10, 25, 67] we have found less than a 5 per cent incidence of any voiding difficulty following the removal of a urinary catheter within 12 to 24 hours of delivery. Evron et al studied a number of urinary function parameters in post-cesarean patients in whom the urinary catheter was removed immediately following surgery.[25] Patients were either treated with epidural morphine, 4 mg, epidural methadone, 4 mg, or non-narcotic analgesics. The group treated with epidural methadone had significantly fewer problems with urinary function than

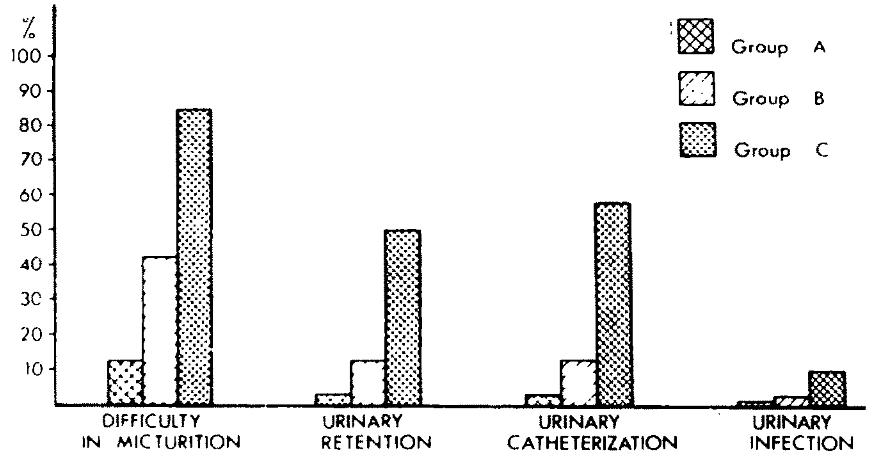

Figure 2. Postoperative urinary problems in three groups of cesarean section patients. Group A received epidural methadone 4 mg; Group B received IM or oral pyramidon 0.5 to 1.0 g; Group C received epidural morphine 4 mg. (*From* Evron S, Samueloff A, Simon A, et al: Urinary function during epidural analgesia with methadone and morphine in post-cesarean section patients. Pain 23:135, 1985; with permission.)

either the epidural morphine or non-narcotic analgesic group (Fig. 2). It has been claimed that urinary retention due to epidural morphine can be reversed with naloxone. This, however, usually requires relatively large doses of naloxone, which may reverse the analgesic effects. The more common and practical treatment is to institute intermittent bladder catheterization as needed.

Respiratory depression is the most serious and feared side effect of epidural narcotic administration. Case reports describing patients with significant respiratory depression appeared soon after epidural and intrathecal narcotic administration was begun in man.[11, 12, 52] In a larger retrospective survey conducted by the Swedish Society of Anesthesiologists, the incidence of ventilatory depression, requiring naloxone treatment, was found to be 0.25 to 0.40 per cent.[30] In a prospective study of 1085 postsurgical patients given epidural morphine for postoperative analgesia the incidence of respiratory depression was found to be 0.9 per cent.[57] A number of factors have been identified that increase the likelihood of developing respiratory depression. These include supplemental parenteral narcotic administration, advanced age, decreased pulmonary function, prolonged surgery in debilitated patients, and possibly the spinal level at which narcotics are administered.[30, 51, 57] Most cases of respiratory depression have occurred within 8 hours of the epidural narcotic administration and may represent direct depression of brainstem centers by narcotic spread within the CSF.[55]

Studies in post-cesarean patients receiving conventional doses of epidural morphine have only rarely identified patients with low respiratory rates or somnolence.[15, 37, 67] In those cases, clinically significant respiratory depression was not believed to be present. It has been postulated that the parturient may be particularly resistant to ventilatory depression because of the increased respiratory drive that occurs during pregnancy.[36] Depressed CO_2 response slopes have been documented in post-cesarean patients following epidural morphine or butorphanol administration.[2] In a prospective study of 1000 patients who were given epidural morphine, 5 mg, for analgesia after cesarean section, Leicht et al noted four patients with respiratory rates of less than ten breaths per minute.[39] Two of these patients were given naloxone, although only one patient was documented to have true respiratory depression. These data represent the most accurate information available in this patient population and indicate that the rate of respiratory depression may be as low as 0.1 to 0.2 per cent.

Although respiratory depression is a serious and potentially fatal complication of epidural narcotic analgesia, we do not believe fear of this problem should preclude the use of this technique in cesarean section patients. For the most part these patients are young, relatively healthy, undergoing short surgical procedures with minimal use of supplementary narcotics or other CNS depressants. When conventional doses of epidural narcotics are used (for example, morphine, 4 to 5 mg), the risks of respiratory depression are very low. Because ventilatory drive has been documented to be depressed for up to 24 hours[2] it is imperative that patients be carefully monitored for at least 24 hours. The use of apnea monitors has been advocated by some; however, in our experience the currently available devices are poorly accepted by patients and are plagued with frequent false alarms. We believe that frequent and careful assessments by specially trained nursing staff represents the best currently available monitor. Respiratory status should be evaluated at 1-hour intervals. It is now recognized that respiratory rate is a poor indicator of ventilatory depression caused by epidural narcotics.[49, 51, 61] Somnolence may be a more reliable indicator of true respiratory depression and should also be specifically evaluated.[50]

A new concern has recently surfaced regarding the use of epidural morphine in cesarean section patients. Two studies have suggested that parturients receiving epidural morphine may be more susceptible to recrudescence of herpes simplex type 1 infections.[20, 28] Postulated mechanisms for this recrudescence include reactivation by local trauma, owing to scratching in response to pruritus, or alteration in the environment at the site of latent virion infection due to cephalad migration of morphine within the CSF. It will be important to substantiate this finding because transmission of the viral infection to the newborn may be possible.

Clinical Application. The optimal dose of morphine for providing analgesia following cesarean delivery appears to be in the 4- to 5-mg range. Most patients given a single dose of epidural morphine, 4 to 5 mg, will not require additional medications for pain during the first 20 to 24 hours following surgery. Many will subsequently require only oral analgesics. If parenteral narcotics are needed, small doses of meperidine or morphine (12.5 to 25 mg or 2 to 4 mg, respectively) will usually be adequate. It has been our experience that patients who have had prior cesarean deliveries with conventional analgesic regimens prefer the analgesia resulting from epidural morphine administration.

Doses of epidural morphine of less than 3 mg have not been demonstrated to provide reliable postoperative analgesia.[18, 54] On the other hand, doses greater than 4 or 5 mg have not been found to provide better analgesia.[14, 54] In some cases the higher doses have been associated with a greater incidence of side effects.[14, 54] Larger doses of morphine will undoubtedly lead to transiently higher concentrations of drug in the blood and potentially better analgesia on that basis. That effect will be short lived, however, and will not provide long-lasting analgesia.

A number of researchers have made the interesting observation that the quality and duration of epidural narcotic analgesia seems to differ significantly depending on the local anesthetic that was used prior to narcotic administration. In particular, 2-chloroprocaine (Nesacaine) given prior to epidural morphine has been found to result in analgesia of shorter duration or poorer quality than that following the use of lidocaine or bupivacaine.[37] Similar observations have been reported when fentanyl was used following 2-chloroprocaine administration.[45] The low pH of chloroprocaine solutions has been considered a possible reason for this observation. However, a recent study using pH-adjusted solutions of chloroprocaine found that alkalinizing the local anesthetic did not affect the quality of subsequent epidural fentanyl analgesia.[42] Another hypothesis that has been put forward is that the analgesia produced by epidural narcotics may not only result from the activation of spinal narcotic receptors, but in addition by a potentiation of an otherwise subclinical effect of the local anesthetic used prior to, or in conjunction with, the epidural narcotic.[31] It is therefore possible that epidural narcotics are less capable of potentiating the subclinical local anesthetic properties of 2-chloroprocaine owing to its shorter duration and more rapid metabolism compared with the other local anesthetics. The mechanism responsible for this phenomenon remains unexplained; however, the observations are being consistently reported and are clinically significant. The practitioner should consider these factors prior to administering epidural narcotics.

Despite the multitude of epidurally administered opioids that have demonstrated potential usefulness for producing analgesia, morphine has remained the most popular for a number of reasons. Morphine is available from at least two manufacturers in a preservative-free formulation, thus minimizing the risk of untoward epidural or subarachnoid cellular reactions. Morphine is, to date, the only narcotic approved by the Federal Drug Administration for use in the epidural and intrathecal space. Epidural morphine provides excellent long-lasting postoperative analgesia from a single administration. Finally, there is extensive published clinical experience that has demonstrated the safety of using morphine in this fashion.

The use of epidural fentanyl for post-cesarean analgesia has also enjoyed some popularity because of fewer side effects associated with its use and the belief that it is less likely to produce respiratory depression. The short duration of analgesia that it produces has limited the use of fentanyl in most institutions. To optimize the administration of fentanyl, continuous infusions appear to be necessary. Infusion rates of 50 to 75 μg per hour provide good analgesia; however, the additional equipment needed for continuous infusions may make this technique impractical for many obstetric services.

Subarachnoid Narcotic Analgesia

The effectiveness of epidural narcotic analgesia following cesarean section has been well established. Numerous reports in the literature since the early 1980s have also documented the effectiveness of intrathecal morphine for the treatment of postoperative pain.[29, 33, 34] Because most regional anesthetics for cesarean section in this country are done with spinal anesthesia,[27] the utility and safety of intrathecal narcotics for managing post-cesarean pain is an important clinical concern. Until recently there has been little information available about this pain-management technique in the post-cesarean population.

We studied 200 post-cesarean patients given intrathecal morphine, 0.3 to 0.5 mg, and compared the analgesia and side effects with that seen in 199 patients given epidural morphine, 3.0 to 5.0 mg.[15] The quality of analgesia was similar in both groups and with all doses studied. The duration of analgesia was somewhat longer in those patients given intrathecal morphine, with 78 per cent of patients not requesting supplemental analgesics in the first 20 hours following surgery. The incidence and severity of side effects were similar in both groups of patients. In our experience, intrathecal morphine in a dose of 0.3 to 0.5 mg provides high-quality post-cesarean analgesia of long duration with side effects comparable to those seen with epidural morphine administration.

Particular concern has been expressed about the risks of late respiratory depression in patients given intrathecal narcotics.[12] Some retrospective studies have indicated a higher incidence of respiratory depression in patients given intrathecal morphine compared with epidural morphine.[30] Abboud et al have studied the ventilatory responses to intrathecal morphine, 0.10 or 0.25 mg, in post-cesarean patients.[1] Minimal changes were seen in ventilatory drive with intrathecal morphine although subcutaneous morphine, 8 mg, resulted in significant decreases in ventilatory drive (Fig. 3). All reported cases of respiratory depression associated with the use of intrathecal morphine, of which we are aware, have involved doses of 1 mg or greater. A number of reports indicate that the quality of analgesia does not seem to improve with increasing doses of intrathecal morphine,[3, 15, 29] indicating a possible ceiling effect for analgesia. Doses less than 0.3 mg do seem to demonstrate a dose-effect relationship.[22,33]

Intrathecal morphine administration has a number of advantages.

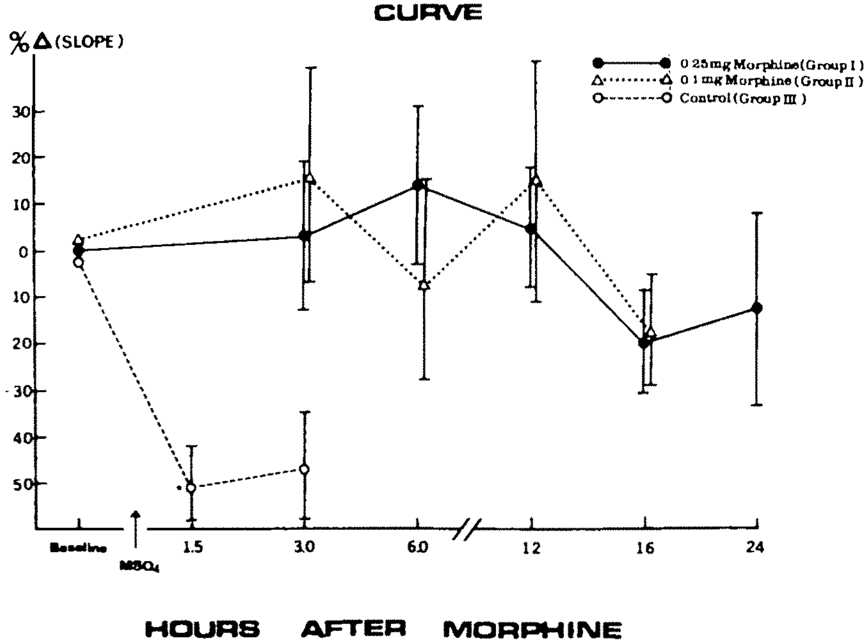

Figure 3. Per cent change in Co_2 response slopes ($L \cdot min^{-1} \cdot mm\ Hg^{-1}$) form baseline values after patients received intrathecal or subcutaneous morphine. (*From* Abboud TK, Dror A, Mosaad P: Mini-dose intrathecal morphine for the relief of post-cesarean section pain: Safety, efficacy and ventilatory responses to carbon dioxide. Anesth Analg 67:137, 1988; with permission.)

It can be given as a one-time dose mixed with the spinal anesthetic solution. The very small doses that are required result in minimal maternal blood concentrations of the drug, thereby minimizing potential narcotic exposure to the fetus. In addition, the potential for narcotic excretion in maternal milk is extremely unlikely. Perhaps most importantly, this route of analgesic administration allows patients having spinal anesthesia for cesarean delivery to have the same quality of postoperative pain control as patients receiving epidural anesthesia.

Clinical Application. Intrathecal narcotic dosages were originally administered empirically. Some of these doses were excessive and often resulted in significant side effects including respiratory depression. It has since been recognized that much smaller doses of intrathecal narcotics can be administered and still provide high-quality analgesia. It is our experience that 0.3 to 0.5 mg of preservative-free morphine administered with the spinal anesthetic solution will provide 18 to 24 hours of analgesia. If additional analgesia is requested by the patient, small doses of parenteral narcotics (meperidine, 12.5 to 25 mg; morphine, 2 to 4 mg) will usually be sufficient. By 24 hours following delivery most of our patients are able to take clear liquids and medications orally, and are easily managed with oral analgesics.

Table 2. *Components of Standard Intraspinal Narcotic Orders*

1. Drug
   (Epidural/ Intrathecal) ______ (drug) ______ mg, administered at ______ (time) ______ (date).
2. Monitoring
   —Respiratory rate and sedation scale q 1 hour for 24 hours following spinal narcotic administration.
   —Respiratory monitor for first 24 hours. Yes ______ No ______
3. Treatment of side effects
   —Naloxone 0.4 mg IV stat if patient found apneic. Call OB Anesthesia stat.
   —Naloxone 0.1 mg IV for respiratory rate less than 10/min; may repeat q 5 minutes X 2; call OB Anesthesia.
   —Diphenhydramine 25 mg PO or IM for severe itching. If not effective, give naloxone 0.1 mg IV; may repeat q 10 minutes X 5.
   —Metoclopramide 5 mg IV for nausea or vomiting; may repeat q 8 hours X 3.
   —For urinary retention, "in and out" bladder catheterization.
4. Miscellaneous
   —Maintain IV access for at least 24 hours after intraspinal narcotic administration.
   —Naloxone 0.4 mg at bedside.
   —No other narcotic analgesics unless ordered by OB Anesthesia.
   —For inadequate analgesia call OB Anesthesia.

Patients who are given intrathecal morphine are managed and monitored in a similar fashion to those given epidural morphine (Table 2).

PATIENT-CONTROLLED ANALGESIA

Recognition of the inadequacies of conventional "as needed" narcotic orders for postoperative analgesia, combined with the goal of reducing many of the unwanted side effects associated with opioids, particularly in the postpartum patient, has led to the development of alternative techniques of narcotic administration. One such method that has recently become very popular is that of patient-controlled analgesia (PCA).

PCA is believed to be more effective than traditional IM narcotic administration because blood concentrations remain fairly constant[21] (Fig. 4). The efficacy of PCA is based on the assumption that postoperative pain control is better with self-administration of small, repetitive, on-demand, IV doses of narcotics than it is with timed, around-the-clock, IM injections. Most authors report that PCA produces better pain relief than conventional IV or IM therapy.[6, 35] A number of preliminary studies have reported that the use of PCAs for postoperative pain relief offered superior pain control with decreased narcotic use,[7] earlier mobilization,[8, 26] and shorter hospital stay[8] when compared with conventional IM therapy. It is interesting that patients using PCAs appear to tolerate mild, nondistressing pain better than patients receiving conventional narcotic therapy. The patients' ex-

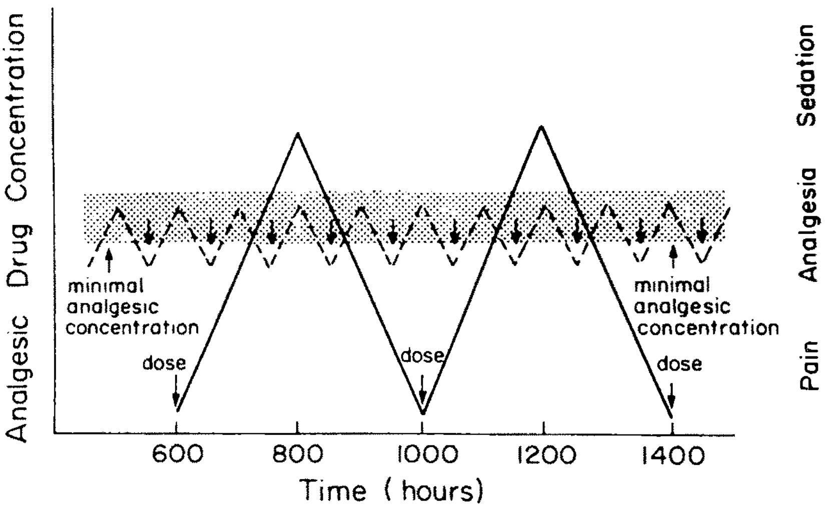

Figure 4. Theoretical relation between analgesic drug concentration, dosing interval, and clinical response for PCA (------) and intramuscular opioid (——). Arrows pointing downward represent administration of patient-controlled or intramuscular opioid doses. (*From* Ferrante FM, Orav EJ, Rocco AG, et al: A statistical model for pain in patient-controlled analgesia and conventional intramuscular opioid regimens. Anesth Analg 67:457, 1988; with permission.)

pectations of some mild postoperative pain balanced against their ability to self-administer analgesia and avoid side effects may explain the satisfaction with PCAs and the consistent observation of not self-medicating to complete pain relief.

The use of PCA devices has risen dramatically over the last few years. They have been received with enthusiasm by the vast majority of patients and nursing personnel; however, their use is not without cost. The machines can be bulky, requiring the patient to manage an IV pole while ambulating, there can be an additional expense to the patient, they can be unintentionally misprogrammed, and narcotic overdosing can occur.[65]

There are few good randomized and controlled studies of the use of PCAs in the postpartum patient. Harrison et al[32] recently reported a group of 18 patients who had undergone elective cesarean section under regional anesthesia. Of these patients, 60 per cent reported only mild pain, 33 per cent reported moderate pain, and only 7 per cent reported severe pain. In a similar study of 30 patients undergoing elective repeat cesarean section, Eisenach et al[24] reported that 40 per cent rated their overall quality of analgesia as comfortable, while 60 per cent reported being only mildly uncomfortable. Of the patients receiving PCA, 90 per cent preferred PCA to other forms of analgesia they had received following prior cesarean sections.

Clinical Application. More than 40 per cent of cesarean sections performed in the United States are conducted using general anesthesia.[27] The parturient who has undergone a cesarean section differs from the general post-surgical patient in that she is greatly influenced by the desire to interact with her newborn. PCA devices are ideally suited for use in post-cesarean patients who have received a general anesthetic. Such devices can provide effective analgesia with a minimum of intrusiveness to maternal infant bonding, as well as a self-determined degree of analgesia and sedation.

Our approach to initiating PCA is quite simple. While in the recovery room, the patient is given sufficient narcotic (meperidine or morphine) to provide adequate analgesia. The patient is then transferred to the ward where PCA is instituted following instruction to the patient in the use of the device. In this way it is ensured that the patient has an adequate loading dose of narcotic and that there will not be a lapse in patient analgesia.

Initial incremental dosing is set at morphine, 1 mg (meperidine 10 mg), per request with an 8-minute lockout interval. If the patient's pain is not controlled after 1 hour, the incremental dose is increased by 0.5 mg of morphine (5 mg of meperidine). If the pain continues to be poorly controlled, after an additional hour, the lockout interval is decreased by 2 minutes. In the vast majority of cases this protocol easily controls the patient's postoperative pain.

We have found that patients who had general anesthesia or who were given PCA devices for other reasons are very satisifed with their analgesic management. A potential disadvantage of the PCA is that with IV administration of morphine, plasma concentrations may fall below analgesic levels more rapidly than following IM administration, thereby resulting in the patient awakening at night with pain and interfering with sleep. This has not been a significant problem in our patient population. Newer PCA devices allow for continuous background infusions, in addition to on-demand boluses of narcotic, in order to circumvent this problem.

PRACTICAL CONSIDERATIONS

Transition from a program of supplying conventional post-cesarean analgesia to a program of delivering intraspinal narcotics or PCA may go smoothly or may be met with significant obstacles. There are a number of basic requirements, which if met, will facilitate a smooth transition. First, a program of thorough nursing education should be established prior to the initiation of new analgesic techniques. The curriculum should include review of nociceptive pathways; actions of IV and spinal narcotics; spinal anatomy; analgesia assessment, instruction in educating patients in the use of PCAs; "trouble shooting" of the PCA devices to be used; patient monitoring skills (use of electronic monitors and patient assessment tools); and a detailed review of the time course for development of side effects and their treatment. Nursing education is best conducted by a clinical nurse specialist who can then serve as a liasion between the nursing staff and the managing

Table 3. *Sedation Scale*

0 = None (alert)
1 = Mild (occasionally drowsy; easy to arouse)
2 = Moderate (frequently drowsy; easy to arouse)
3 = Severe (somnolent; difficult to arouse)
S = Sleep (normal sleep; easy to arouse)

physicians. One cannot overemphasize the importance of nursing education prior to the implementation of these new techniques. Second, it is essential that a physician be available at all times to respond to questions or medical problems that may arise. This person should be the only one responsible for the analgesic and sedative medications that these patients are to receive. Finally, protocols should be developed, including uniform orders, to promote a consistent standard of care and communication between the nursing and physician staff. These protocols must be tailored to the medical preferences, nursing practices, and the patient population served at a given institution.

Monitoring requirements have been the single most important issue faced by institutions embarking on the use of these new techniques. Monitoring practices have undergone a significant evolution over the past few years at our institution. We feel that obstetric patients who have received epidural morphine can, for the most part, be managed safely with standard protocols and orders. The essential components of our standard set of orders are reproduced in Table 2. The development of respiratory depression in patients receiving spinal narcotics is probably the most worrisome aspect of the application of this pain control technique. We have found that electronic monitoring of respiratory rate has not been necessary for the vast majority of our patients. Assessment of respiration and sedation by a trained nurse, on an hourly basis, has been of greater value. By having the nurse evaluate the respiratory status of the patient one not only obtains information about the rate, which in and of itself may not be a good measure of impending respiratory failure, but also of the adequacy of respiratory efforts. An additional piece of information we have found most helpful is the patient's level of sedation. The sedation scale that we use is reproduced in Table 3.

SUMMARY

A recent survey by Gibbs et al[27] indicates that of the cesarean sections performed in this country 41 per cent are conducted using general anesthesia, 34 per cent are conducted using spinal anesthesia, and 21 per cent are conducted using epidural anesthesia. This survey identifies three separate populations of patients and three different routes by which we may tailor the patient's postoperative analgesia. These routes that involve epidural, intrathecal, and patient-controlled

IV analgesic administration are gaining in popularity and are replacing traditional IM analgesics.

It has become clear over the past few years that intraspinal narcotics and PCAs can provide the post-cesarean patient with superior analgesia compared with IM narcotics.[24, 32] It has also become clear that these techniques can be delivered safely with very little risk to the patient, perhaps no greater than conventional analgesic techniques. The benefits of these new techniques is not limited to better analgesia. Patients given epidural morphine following cesarean section become ambulatory earlier than those given IV morphine for relief of pain.[17] Epidural opiate analgesia has been shown to reduce morbidity in high-risk surgical patients and thereby improve outcome.[48, 69] There is also evidence that even the low-risk cesarean section patients given intraspinal morphine for postoperative pain relief may have a shorter hospital stay than those given IV and IM narcotics.[56] Finally, recent studies by Harrison et al[32] and Eisenach et al[24] have compared IM, PCA, and epidural narcotics for providing post-cesarean analgesia. They demonstrated that, in terms of providing analgesia, PCA was superior to IM narcotics, and that epidural narcotics were superior to PCA. A surprising finding, and one that deserves further study, was that even though those patients given epidural narcotics reported better analgesia than those given IM or PCA, those patients given PCA reported higher levels of satisfaction compared with prior cesarean deliveries than those patients given epidural narcotics.[24] Again, it is not a direct comparison but an implied or inferred comparison. Thus, in those instances when epidural or intrathecal narcotic administration is impossible or undesirable, PCA can provide an attractive alternative, offering excellent analgesia and a high degree of patient satisfaction.

In this article we reviewed the analgesic options available for the post-cesarean patient and attempted to outline the risks, benefits, and implementation of three new techniques for providing analgesia. With each new year these techniques have been finding, and will undoubtedly continue to find, wider clinical application, thereby improving the care for women having cesarean deliveries.

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Postoperative Pain Management in Children

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Over 3 million children undergo surgery each year in the United States,[29, 39] and the available data indicate that pain management in children, as in adults, is often inadequate.[9, 28] One might wonder why pain management is inadequate, when, in fact, relief of suffering is one of the goals of medicine. Based on studies of adults, one can infer that a significant part of the problem is the routine use of a fixed dose of narcotic, ordered to be given as needed and given by an intramuscular injection. Similar sorts of pain management are used in children and contribute to the inadequacies of postoperative pain management in children. Imagine what goes through a 5-year-old child's mind when the nurse approaches with the instrument most often feared by children—a syringe and needle—and tells the child that this shot will produce relief of pain, after a period of time. The nurse gives the shot, the child suffers the pain of injection, and, not surprisingly, does not feel better. Later, when the narcotic begins to take effect, the child is not convinced that the injection had anything to do with relief of pain. This scenario, when analyzed for its behavioral components, reveals a situation in which the child's complaint of pain is followed by an aversive stimulus. One would expect the child to reduce the frequency of pain complaints. That result makes things quieter on the ward for the nursing staff, but the child suffers pain quietly and, as a result, gets inadequate treatment. Such a phenomenon is common in children's hospitals.

In addition to the routine use of a fixed prescription of intramuscular narcotic, there are other factors that contribute to inadequate pain treatment in children after surgery. One is the incorrect belief that children do not feel pain, or if they feel it they do not remember it. There is no credible evidence that children do not feel pain, and

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in the absence of evidence, humanitarian concerns suggests that we should treat pain. Another contributing factor is lack of specific knowledge about the assessment, physiology, pathophysiology, and treatment of pain in children. Excessive concerns about side effects of narcotics and about addiction also result in the current undertreatment of children after surgery.

In this article, the physiology and pharmacology of pain transmission, the response of the patient to pain, and the effects of untreated pain are addressed. We first discuss the special problems of infants, because infants present unique concerns, and then follow with a general discussion of techniques of pain control.

PHYSIOLOGY AND PHARMACOLOGY

Pain is a perception that is far more complex than simple transmission of information along nerve pathways to the brain. It consists of a component of transmission of pain sensation, a component of processing and evaluation by higher centers of the brain, and a component of reaction to the sensation. While the pathways of nerve transmission to the brain are complex in themselves, it is the evaluation, processing, and reaction to the pain sensation that are the major source of complexity and that account for the wide variability in response to pain among patients. To try to identify some of the specific problems associated with pain in children, we will briefly discuss each of these components, namely pain transmission, the psychological components of processing and evaluation, and the responses to pain, but for a full discussion the reader is referred to more comprehensive references.

In the periphery of the nervous system are located nociceptors that respond to pain and inflammation. The nociceptors are specialized units that respond to strong pressure, heat, cold, irritant chemicals, or other stimuli. Some mediators of inflammation such as prostaglandins, bradykinin, 5-hydroxytryptamine, histamine, and acetylcholine can serve as excitors or modulators of the painful stimulus. There is no specific information about the changes that occur in these systems during human growth and development, and the effects that development might have on peripheral pain receptors are unknown. The painful sensations that arise in the periphery are transmitted to the spinal cord via A delta and C nerve fibers (small myelinated and nonmyelinated fibers), and these fibers enter the substantia gelatinosa of the spinal cord. Here many synapses occur, and it is felt that much modulation of the pain sensation occurs at this point. Modulation may occur from the influence of other input into the area, that is, from descending nervous input or from other peripheral input. It may also result from the effects of chemical modulators such as the endogenous opioid system, or from the psychological influences that modulate pain. It is in this area of the nervous system also that opioids are felt to have a major effect in reducing the perception of pain.

After the pain sensation passes through the substantia gelatinosa, it ascends to the brain via the anterior spinothalamic tract and other ascending tracts. In the brain the sensation traverses the thalamus and projects to the cerebral cortex.

The psychological influences that alter a patient's response to pain are complex and could be the subject of a book themselves. Suffice it to say that in adults such factors as the context of the pain and its meaning to the patient may alter a patient's perception of pain. When one considers children, the child's developmental stage and family interaction are further major factors that influence a child's response to pain. In addition, age, cognitive ability, the child's trust of the caregivers, and previous painful experiences will also influence their response. The manner in which the family deals with the stress of a child's illness and pain will also influence what the child feels. All of these factors may also influence learning about pain, and may alter the way a child deals with pain in the future. Appropriate preparation, sympathetic handling, and careful management are therefore of even greater importance when dealing with children, because the way a child is treated may influence the way he deals with pain for the rest of his life.

The response to pain consists of behavioral, psychological, and social changes that will be discussed. In addition to the behavioral and social aspects of pain, other responses occur that alter pain sensation. Segmental and suprasegmental reflexes may alter pain perception. Segmental reflexes arise at the level of the spinal cord and may lead to muscle spasm and increased pain, and to alterations of respiration, circulation, and other organ function. Some of these changes may arise from activation of the sympathetic nervous system.[6]

Suprasegmental reflexes arise from stimulation of higher medullary or autonomic centers, with subsequent alteration of respiratory or circulatory function. In addition to these reflex responses, pain can produce an endocrine stress response, leading to secretion of hormones such as epinephrine, norepinephrine, ACTH, cortisol, growth hormone, ADH, glucagon, and aldosterone, and a decrease in secretion of insulin and testosterone.[6] If unmodulated, the stress response may lead to complications that slow a patient's recovery and that could potentially be fatal. The harmful effects of this response are discussed in the following section.

EFFECTS OF UNTREATED PAIN

Untreated pain can lead to physiologic complications, psychologic distress (which can lead to personality changes in developing children), family disruption, interruption of hospital routine, and prolongation of hospitalization with resultant increased costs. It may be hard to separate all the harmful effects of hospitalization and surgery per se from those of pain in any individual child, but inadequately treated pain can clearly color a child's hospital experience and may account for many adverse effects. We will discuss each of these effects of untreated pain.

It is clear that adverse physiologic consequences arise in association with untreated pain. Following upper abdominal surgery or thoracic surgery, pain can lead to splinting, ineffective coughing, and potentially to atelectasis and pneumonia.[4, 5, 12] While data are lacking in children, studies in adults indicate that after upper abdominal surgery, there is a decrease in functional residual capacity (FRC),[26, 40] a decrease in inspiratory and vital capacity, and a fall in arterial oxygen tension.[37] Several factors in children may accentuate these problems. Young children have more compliant chest walls,[30, 33] may require muscle activity to stabilize the chest wall during inspiration, and therefore may be more prone to muscle fatigue. FRC may fall further in children. Closing volume is greater than FRC in young children,[27] and thus the child with a fall in FRC may be particularly susceptible to the development of hypoxemia. Compared with adults, oxygen consumption is relatively higher, and alveolar ventilation is relatively greater, accentuating the problems of hypoxemia associated with pain in the postoperative period. Adequate pain therapy will allow the patient to cough and take deep breaths, and to some extent reduce the harmful effects of surgery and pain on respiratory function.

Mobilization of the stress response can lead to an increase in catecholamine secretion, with increased oxygen consumption, increased cardiac work, and tachycardia. If catecholamine secretion continues at a high rate, it can lead to a reduction in caloric reserve needed for healing.

Psychologic distress may arise in a child just from being in a hospital and separated from parents, and if untreated pain is added to this background, the psychologic result may be devastating. The exact response to some extent will depend on the age of the child. Pain can lead to anxiety and a loss of a sense of control. This can be particularly harmful in those patients who are at a developmental stage where they are learning self-control, namely the early school age child. The child's social relationships may also be harmed. In young burned patients a condition of "learned helplessness" has been described in which children withdraw from their environment and stop participating in interpersonal interactions.[14] In addition to social withdrawal, one may see behavioral regression, temper tantrums, and demanding behavior. These reactions to pain may permanently alter the way a child learns to deal with the world.

Family disruption may occur. Families are under considerable stress with children in the hospital, and if the child also has inadequately treated pain, the stress on the family may increase and magnify any tension and social pathology already present.

For the hospital staff, a child in pain presents a problem. The staff's duty to patients requires that the child be treated, and the staff is frustrated if those in charge of the medical care are unwilling to treat the pain or do not know how to treat the pain. This frustration can lead to disagreements among the health care team, and these disagreements can be among the most virulent encountered in the hospital setting. Other staff may use cognitive restructuring of the situation and espouse the belief that the child is not feeling pain, is faking, or is using pain behavior to manipulate the situation. Physicians may be frustrated because of a desire to treat pain, while a perceived lack of a safe technique prevents effective treatment of pain. Inordinate amounts of time may be expended discussing the untreated pain, and other factors in the patient's care may be neglected in the conflict arising out of inadequately treated pain. In addition, the crying out or moaning of a patient in pain can upset the hospital routine and produce distress in other patients and families.

All of the factors discussed previously can lead to prolonged hospitalization and increased costs. A recent study compared a group of adult patients who had anesthesia with one technique (epidural local anesthesia and light general anesthesia and postoperative pain control with epidural local anesthetics or opioids) to a group of patients treated with standard general anesthesia and conventional parenteral opioids.[41] The group with epidural anesthesia and epidural postoperative pain control had fewer postoperative complications and reduced hospital costs compared with the patients who had conventional treatment. Although the fewer complications and reduced hospital costs cannot be attributed entirely to better postoperative pain control, it is likely that better pain control was a major influence in the outcome.

PAIN ASSESSMENT

As for adults, there are no physiologic or laboratory methods of measuring pain intensity in children. And because of the developmental, cognitive, and emotional differences between adults and children, pain assessment is even more difficult in children. Generally, there are two types of techniques that are useful for pain assessment: self-report and observation of behavior. Variations of these techniques are useful for estimating pain intensity in children.

The simplest and most accurate method of self-report of pain intensity in adults is a visual analog scale (VAS). This is most often a 10-cm line without divisions, with the words "no pain" on one end, and the words "worst pain possible" on the other. The patient is instructed to make a mark on the line, the position of the mark indicating the intensity of the pain. A variation of this technique is a scaling technique in which the patient estimates pain intensity by selecting a number from zero to ten, zero indicating no pain. Use of this technique presupposes an understanding of the number system, or at least an understanding that one quantity can consistently be greater than another. The VAS and its variations have proven useful with children over the ages of 6 or 7 years, and reasonable validation data are available in this group.[1, 24, 34]

Pain assessment is more difficult in patients under age 6 years.

They usually have not developed the cognitive skills necessary for use of the VAS or a numerical scaling system, and thus very crude methods of self-report must be used, and the bulk of pain intensity estimation occurs via interpretation of behavior. The methods of self-report rely on cooperation of the child, which may be lacking in the strange setting of the hospital after parents have been sent away and a painful operation has been inflicted on the child. The methods that are available include the Smiley Analog Scale, Poker Chip scale, and color scale. In the Smiley Analog Scale, the child is asked to select, from a series of pictures of faces, the one that depicts how he or she feels now. Some investigators have been able to obtain data with this scale,[8, 24] but it can be very difficult to use with a child in pain who is unfamiliar with the examiner—the situation most often found in the postoperative situation. It is also difficult to determine whether it is pain, hunger, anxiety, or some other emotion that the child is reporting.

Behavior observation is most often used in the preverbal child, and is often necessary in children who have verbal skills but who are too young to use a VAS. One method of behavioral observation is the CHEOPS scale,[25] in which an observer notes six aspects of the child's behavior and a numerical rating is applied to each. These scores are added, and the total score estimates pain intensity. This scale has been tested in postoperative children, and has been found a useful measure of presumed pain.[25] We have used a simple 5-point estimation of behavior as a key for determining need for postoperative pain medication and have found it useful,[16] but validation studies are not yet completed. We score 1 point for a child who is laughing and playing, 2 points for a child who is happy, 3 for one who is neutral, 4 for crying or other behaviors indicating pain from which the child can be distracted, and 5 if the child cannot be distracted. Pain medication is administered if the child scores 4 or above. Other observational scales are also available.[13] In the hospital setting, pain is often assessed by use of unstructured observation by the staff, a practice that may often lead to mismanagement of pain.

For the reader who is interested in a more in-depth discussion of pain assessment, several recent reviews are available.[10, 22, 23]

TREATMENT OF POSTOPERATIVE PAIN IN INFANTS

Infants have historically been treated differently than adults because it has been assumed that they do not feel pain, or if they indeed feel pain, they do not remember it. These attitudes are becoming less prominent as evidence evolves that infants do feel pain and that harmful physiologic effects arise as a result of untreated pain.[2] Clearly, the areas of the higher nervous system necessary for conscious perception of pain are present in newborns, and there is evidence by PET scan that these higher centers are active.[11] The fact that facial expressions characteristic of the emotional responses to pain are produced in young infants is further evidence that high nervous system centers are functioning. That habituation and operant conditioning occur is evidence that memory is present.[19] Studies of infants undergoing surgery with very light anesthesia indicate that with pain, endocrine stress responses occur (release of epinephrine, norepinephrine, cortisol, and so forth), and that these stress responses lead to an extended catabolic period following surgery, with a higher number of complications than are seen with deeper anesthesia.[3]

Given that infants feel pain, that it affects behavior, and that the stress response indicates that there are valid physiologic reasons to treat pain, one might ask what obstacles stand in the way of effective treatment of postoperative pain in infants. The two primary obstacles are the inadequate methods available to assess pain in the preverbal child and the increased risks associated with parenteral narcotics.

Pain assessment is a major challenge. We must rely on subjective evaluation of the patient's behavior. Although several behavioral scoring systems are now available, they are not well standardized or validated in infants. Attempts have been made to quantitatively describe the type of cry that a baby emits,[18] but it is difficult to correlate any particular type of cry with pain unless the context of the situation is taken into account. Investigators have attempted to evaluate facial expression,[31] and although it is clear that facial expression does correlate with presumed pain, determination of intensity is difficult. Often, rather than any specific pain-scoring systems for pain, nurses who have to make decisions about pain in spite of inadequate information rely on intuition and clinical experience as indicators of pain in infants.

The other major impediment to treating infant pain after surgery is the lack of safe methods to do so. Narcotics are fraught with hazard in infants, and major textbooks suggest avoiding them unless the babies are to be mechanically ventilated. The evidence on which this recommendation is based comes from several sources. The clinical experience of pediatric anesthesiologists suggests that respiratory complications are more frequent in infants than in older patient after opioids are given. Evidence that narcotic clearance is prolonged in infants compared with older children[21] is another reason. This prolongation of clearance can lead to unexpectedly high levels of narcotic drugs in blood and greater risk of respiratory depression. Finally, it has been shown that in infant rats, narcotics cross the blood-brain barrier more rapidly than in adult rats.[17] If this finding is also true in human infants, more narcotic may get into the brain and lead to a higher incidence of CNS depression.

These potential problems and the lack of any comprehensive methodologic studies of postoperative pain control in infants make it difficult to make credible recommendations about postoperative pain management. If an infant is to be mechanically ventilated after surgery, the solution becomes obvious. Use opioids in sufficient doses to abolish pain, and after the narcotic has cleared, wean the infants from the ventilator with caution. If the baby is not mechanically ventilated, then most pediatric anesthesiologists recommend acetaminophen in doses of 5 to 10 mg per kg every 4 to 6 hours. If this does not provide sufficient pain relief, then some recommend codeine and others would cautiously use morphine in low doses with careful monitoring for apnea, which may be the earliest finding of respiratory complications in this age group.

TREATMENT OF PAIN IN CHILDREN OVER 6 MONTHS OF AGE

Narcotics

In adults, one of the major problems in managing postoperative pain is that narcotics are ordered to be given every 4 hours in doses that are marginal or inadequate. This sort of treatment plan may lead to a period of effective pain relief. Shortly thereafter, however, the blood level of the medication falls below the effective level, pain returns, and the patient must suffer until the next dose is available. Given the half-life of the narcotics and the usual 4-hour administration, this wait can be a period of several hours. The way to avoid this problem is to give smaller doses more frequently, assess the patient's response, and adjust the dose according to the patient's need.

The mainstay of treatment of postoperative pain in children is parenteral narcotics. Especially with children, the intramuscular route is undesirable. Children will deny pain for fear of receiving an injection, and attention has therefore turned to potential alternatives to the traditional intramuscular approach. Sublingual, rectal, and transdermal routes are being investigated, but appropriate preparations are not yet generally available for children. Therefore, the intravenous route is preferred, if adequate nursing observation is available, and the doses are given frequently enough to provide effective pain relief.

The choice of drug is often made on the basis of clinical experience and habit, with little thought about the reason for a choice. Morphine has the advantage of great clinical experience and economy. It is the standard against which all other narcotics are judged. Starting doses for children are 0.05 mg per kg intravenously and 0.1 mg per kg intramuscularly. Side effects occur with morphine, as with all other narcotics, but the incidence of these side effects has not been well studied. Meperidine is a synthetic opioid that is frequently used for postoperative analgesia. Its half-life is much shorter than one might imagine from the usual 4-hourly prescribing habit. As with morphine, side effects occur, but no good data are available to compare meperidine with other narcotics. Some clinicians believe that morphine has more side effects, and some believe that meperidine has more side effects associated with its use. No scientific data are available to settle this dispute with regard to children.

Morphine is metabolized (glucuronidated) by the liver and then the metabolic by-products are excreted by the kidneys. Meperidine is metabolized to normeperidine, which is a centrally active compound that is excreted by the kidneys. The accumulation of meperidine metabolites may lead to CNS activation manifested as delirium, agitation, or seizures. For this reason, meperidine is avoided in the patients who might fail to excrete the metabolites, specifically patients with renal impairment.

Other synthetic narcotics are now available. These drugs are more receptor specific and therefore have the potential advantage of providing better analgesia with fewer side effects. The disadvantage of these drugs is that they are short acting and expensive, and therefore are not well suited for providing postoperative pain relief. Fentanyl is the most commonly used of these agents. It can be used as a continuous infusion for postoperative pain relief. Because it does not cause histamine release, as do morphine and meperidine, it is especially useful for those patients who are susceptible to adverse effects from histamine release, such as patients with asthma. Fentanyl is not labeled for use in children under 2 years of age. Other synthetic narcotics that have recently been released are sufentanil and alfentanil. Both are potent, short-acting agents with minimal cardiovascular side effects. Sufentanil is not labeled for use in children under 2 years, and alfentanil is not labeled for those under 12 years. Higher doses of these agents may cause skeletal muscle rigidity, a condition that is particularly dangerous when the muscles of the chest wall are involved, because the treatment (if one is needed) is a nondepolarizing muscle relaxant, the use of which necessitates mechanical ventilation.

Because some physicians continue to use only intramuscular injections for pain relief, perhaps because of misconceptions about side effects or risks of intravenous narcotics, investigators have searched for a technique that could minimize the number of injections used. Methadone has long-lasting analgesic effects. The use of methadone as part of the anesthetic in the operating room has been tested as a way of providing long-lasting postoperative analgesia.[7] The use of methadone (0.2 mg per kg) at the start of anesthesia provides postoperative analgesia for periods of up to 36 hours. This technique thus can obviate intramuscular injections for a prolonged period after surgery. The potential hazard with methadone is largely that of its long-lasting effect—an actual or relative overdose will be long lasting also.

Codeine is sometimes used to provide moderate analgesia when the physician wishes to avoid other potent narcotics, or to use an agent by oral administration. Its analgesic efficacy is thought to be about the same as aspirin or acetaminophen when given orally, but it does have an additive effect with these agents and can be used with advantage along with them. Side effects with codeine have not been well studied, but with intravenous use these may include flushing and hypotension, possibly related to histamine release.[35]

Non-Narcotics

These drugs include acetaminophen, aspirin, and the nonsteroidal anti-inflammatory agents (NSAIA).

Acetaminophen is a drug that is effective for mild to moderate pain in both adults and children. Children's preparations are available, and are frequently used for pain relief in children of all ages. The major side effects and problems are those of a massive overdose, which can lead to fatal hepatic necrosis if untreated.

Aspirin is effective in providing pain relief, but has side effects and possible toxicities that now limit its use in children following surgery. Aspirin inhibits platelet aggregation and may lead to impaired coagulation; therefore, it is rarely used before or after surgery. In addition, the use of aspirin has been associated with the development of Reye's syndrome,[32] a potentially fatal liver dysfunction of children and adolescents. Aspirin today is therefore used much less frequently for treatment of pain in children and adolescents.

NSAIAs are effective in relieving mild to moderate postoperative pain in adults, and are starting to be used in children. None are labeled for pediatric use. There are no parenteral preparations and satisfatory rectal preparations are not available, thus the use of NSAIAs is limited to those patients who are able to take them orally. This limitation usually precludes use immediately after surgery, but the drugs may be useful for some patients who are able to begin oral intake soon after surgery. Another approach is to begin NSAIAs prior to surgery, and continue with them when oral intake is reestablished. This strategy may be useful in the outpatient surgery setting.

Behavioral Treatment

Behavioral treatment involves both creating a comfortable environment for the child during the surgical period, and also active measures that may be useful for older children.

Good preoperative preparation of the child is important. He or she should be informed in a nonthreatening way about what will happen during the surgical period, that separation from parents will be minimized, and that pharmacologic pain relief is available if needed. One educational approach is the use of puppets or dolls at a formal preoperative preview of the hospital. If possible, specific fears (such as the child equating being put to sleep with what may have once happened to a family pet) need to be determined and discussed. Minimizing separation of the child from his or her family is helpful in reducing many of the anxieties that can increase a child's perception of pain.

With respect to behavioral pain management techniques, distraction techniques, such as listening to headphones or stories told by staff or parents, can be helpful. One active technique that can be taught to a child is progressive muscular relaxation. The rationale for this approach is that pain and anxiety may lead to muscle tension that can amplify pain. The child is taught to produce deep muscle relaxation prior to surgery and then uses this technique to reduce pain after surgery. Meditation may also be taught to produce a state of deep relaxation. Mental imagery or self-hypnosis is frequently useful in children, who can be excellent hypnotic subjects. The child is taught to develop a mental image of comfort in the affected part of the body. For a painful limb the suggestion might be made to think of the limb immersed in a cold stream or to imagine the limb to be floating free on a cloud.

NEW TECHNIQUES OF PAIN CONTROL

The methods of pain control just discussed are considered the conventional approach to postoperative pain. Recently, several advances have occurred that have improved pain control for adults and that can, to some extent, be applied in children. These techniques are continuous intravenous infusion of narcotics, patient-controlled analgesia (PCA), and epidural administration of narcotics. These techniques will be discussed briefly, and their use in children will be specifically examined. For a more thorough discussion of the techniques, the reader is referred to other sources.

Continuous Intravenous Infusion

To avoid the fluctuating blood levels of narcotic that occur with the use of parenteral opioids, continuous intravenous infusion of opioids can be used. Prerequisites for this technique are excellent nursing coverage to evaluate for signs of excess narcotic effect and a reliable method of providing a constant infusion rate of narcotic. Our clinical approach is to use a loading dose of narcotic sufficient to make the child comfortable (for example, morphine 0.05 to 0.1 mg per kg or more if necessary) and then to begin a continuous infusion of morphine starting at a rate of 10 to 20 μg per kg per hour, subsequently adjusted according to patient need.[20]

Patient-Controlled Analgesia

PCA is a technique of narcotic administration that is based on the premise that a patient is the best judge of how much narcotic he or she needs and how often it should be given. The technique uses a sophisticated IV pump that allows the patient to self-administer narcotic within parameters ordered by the physician. When the patient pushes the button, the IV pump delivers a small bolus of narcotic. The machine then goes into a lockout period during which the patient cannot administer more narcotic. The physician determines the size of the bolus, the duration of the lockout interval, and an hourly or 4-hourly limit of total narcotic use. For a typical adult patient, the bolus dose is set at 1 to 2 mg of morphine, the lockout at 6 to 10 minutes, and the 4-hour limit at 10 to 15 mg. Use of this machine allows the patient to control their own narcotic use and to treat pain when it occurs, not according to the pre-set hospital schedule. The use of small frequent boluses of narcotic allows the patient to maintain a more constant blood level of narcotic, thus avoiding the cycle of sedation-analgesia-pain so commonly seen with bolus parenteral narcotic administration.

We have reported our experience with PCA in 25 adolescent patients following surgery.[38] The patients, aged 12 to 19 years, used the machine responsibly, did not overdose, and were satisfied with their analgesia. Those patients who had prior surgery uniformly preferred PCA to conventional techniques. When medication patterns were examined, the remarkable things noted were the wide variability in narcotic use among patients (as much as eight times variability in hourly morphine use, after normalizing for body size), and the fact that most patients did not titrate themselves to complete analgesia, rather, they maintained a slight degree of pain, perhaps titrating pain relief against side effects of medication. There were no episodes of clinical respiratory depression.

We now routinely offer PCA to patients 12 years old and above if they are of average intelligence, understand the concept, wish to use the device, and have no prior history of drug abuse. In the postoperative recovery room, the patients are medicated to comfort by an anesthesiologist with IV narcotic, and PCA is begun while the patients are still comfortable. Typical orders with morphine are dose, 0.015 mg per kg; lockout, 10 minutes; and 4-hour limit, 0.25 mg per kg. In each instance a member of the anesthesiology department is identified to respond to problems, to adjust doses, and to visit the patient daily to evaluate pain control.

Epidural Narcotics

The use of narcotics administered into the epidural space has achieved widespread use in adults, but there has not been extensive experience in children. The technique makes use of the fact that opioid receptors are found in the substantia gelatinosa of the spinal cord, and administration of opioids into the cerebrospinal fluid or the epidural space leads to occupation of these receptors by the narcotic, which in turn leads to a diminution of pain transmission.. The pain relief obtained is not sufficient to provide surgical anesthesia, but is sufficient to make most patients quite comfortable during the postoperative period. In addition to the good quality of pain relief, advantages of epidural narcotics are that they do not alter motor power and do not affect sympathetic nervous system function. Thus, patients can sit up without postural hypotension, and may ambulate in a fairly painfree state.

This technique has been used in children in whom it has been shown that the pain relief obtained is longer lasting than with either IV morphine or epidural bupivacaine.[16] Several aspects of the technique are different in children.

Our indications for epidural narcotics are pain of moderate to severe intensity, for example, following a thoracotomy, an upper abdominal incision, genital surgery, or lower extremity orthopedic surgery. A catheter is placed in the epidural space to allow repeat doses. The catheter can be placed in either the lumbar epidural space or in the caudal space. The caudal space has much to offer in children; it is simple to locate in children and reliable results can easily be obtained. Lumbar epidural catheters are somewhat more difficult to insert, especially for those who are not used to performing this technique in smaller children.

The epidural catheter may be used for anesthesia during surgery, or if the anesthesiologist prefers, general anesthesia can be given. We avoid concomitant parenteral narcotics during the anesthetic to try to reduce the risk of postoperative respiratory depression. Epidural morphine should be administered at least a half hour prior to the end of surgery to allow time for the relatively slow onset of pain relief to occur. We use a dose of 0.033 to 0.050 mg per kg of morphine. It is clear that some patients will not have prolonged analgesia with this dose, but it is our belief that as the dose increases, so does the risk of respiratory depression.

Morphine is the drug that is used most commonly. It is available as a preservative-free preparation (Duramorph, Elkins-Sinn Inc, Cherry Hill NJ; Astramorph, Astra Pharmaceutical Products, Westboro, MA) but neither is labeled for use in children under 13 years. Some investigators have suggested that a lipophilic drug such as fentanyl or sufentanil might be preferable to morphine, because less might dissolve in and migrate in the CSF, and therefore not ascend to the brain leading to side effects. Fentanyl has been used in adults, but data are not available to support the hypothesis that side effects are reduced. Fentanyl does have the advantage that it has a short onset of action and therefore may be helpful in those instances when a more rapid onset of analgesia is desired than is obtained with morphine.

Reinjections of the same dose of morphine are made when the patient begins to experience pain again. If inadequate pain relief or inadequate duration of pain relief has been seen, the dose is increased at the time of reinjection.

Side effects in children are similar to those seen in adults, in particular itching, nausea and vomiting, urinary retention, and delayed respiratory depression. Itching is often more of an annoyance than a major problem, and if it is necessary to treat the itching, one can use Benadryl. If that is not helpful, a low dose of naloxone (0.005 mg per kg) will abolish the itching with little or no diminution of analgesia. Nausea and vomiting occur, but the incidence is not clearly known in children. Our usual approach is to use metoclopramide, and if that is not successful, then low-dose naloxone (0.005 mg per kg) is used. Urinary retention may be a problem, especially in genital surgery if a urinary catheter is not to be left in place; in that situation we would choose an alternative method of pain relief. Although these side effects can be problems for some patients, the major concern about epidural opioids is the problem of delayed respiratory depression.[15] This can happen in children, is possibly related to dose, and mandates respiratory monitoring of the patient. If it occurs it can be treated with naloxone (0.01 mg per kg) without reversing the analgesia.

Because of the possibility of delayed respiratory depression, which may occur up to 12 hours after injection, we monitor all patients treated with epidural opioids with apnea monitors and cardiac mon-

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itors. Data from adults indicate that the most effective monitor is an alert nurse watching the patient's state of consciousness. To avoid the problems of delayed respiratory depression we do not use concomitant parenteral opioids during anesthesia or during the postoperative period when epidural opioids are used. Other monitoring devices that may be of use are the pulse oximeter and a capnograph to monitor end-tidal CO_2. Data are not available, however, to indicate that these techniques will be effective in detecting severe and dangerous respiratory depression.

Regional Anesthesia

Regional anesthesia is useful in some situations for providing postoperative analgesia. Iliohypogastric and ilioinguinal nerve block with bupivacaine is useful after herniorrhaphy and orchiopexy.[36] This block can be performed by the surgeon while the wound is open using 0.25 to 0.5 per cent bupivacaine, 1 to 2 ml.

Dorsal nerve block of the penis is effective in providing postoperative pain relief after circumcision. In addition it has been shown that 2 per cent lidocaine jelly applied to the penis provides effective analgesia after circumcision.

SUMMARY

Postoperative pain management is a topic that has been neglected but is currently an active field. In children, pain transmission is not fully understood, but may be affected by the child's state of development. Clearly, the child's cognitive understanding of pain and emotional response to pain are different than an adult's. These differences make pain assessment more difficult, but workers are developing techniques that may be helpful in estimating pain intensity in children. The effects of untreated pain in children are similar to those in adults, but the effects may be more significant. Pain treatment is often inadequate after surgery in children, but newer techniques such as continuous infusion of narcotics, patient-controlled analgesia (PCA) and regional analgesia techniques such as epidural narcotics hold promise for the future.

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Psychological Strategies in Acute Pain Management

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Pain researchers and clinicians are increasingly aware of the role of psychological variables in moderating both acute and chronic pain. With the advent of the gate-control theory of pain, it has become widely accepted that there is not necessarily a direct correlation between extent of organic injury and pain expression.[23] Peck[24] exhaustively reviewed the literature on pain and psychological variables, noting that variables such as expectation, attention versus distraction, cognitive appraisal, observational learning, fear and anxiety, individual coping style, and perceived control over pain can affect both the patient's report of pain and overt pain behaviors, including the use of opioid analgesics. The role of these psychological variables as intervening factors in pain is discussed elsewhere in this volume and so will not be addressed specifically here. However, increasing awareness of these variables has led to the application of psychological strategies in an effort to modify the variables and thereby ameliorate or prevent excessive pain control problems. This article reviews the strategies that have been used to achieve better pain reduction in the acute pain setting.

The use of psychological interventions in pain management has been most widely applied within the chronic pain setting where behavioral strategies have resulted in a revolution in the approach to treatment. These strategies have been less widely researched and applied in acute pain settings, although research and clinical efforts have included burn pain, postsurgical pain, and procedural pain. Additionally, laboratory analogues within the research literature are numerous. The modest number of controlled clinical trials suggests that

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Table 1. *Psychologic Interventions for Acute Pain*

- Information provision
  - Sensory
  - Temporal
  - Procedural
- Cognitive coping strategies
  - Cognitive appraisal
  - Attention versus distraction
- Relaxation and related techniques
  - Deep breathing
  - Muscle relaxation
  - Imagery
  - Hypnosis
- Increased perceived control
  - Stress inoculation
  - Patient-controlled analgesia
  - Instruction in effective self-care activities

acute pain can be modified by behavioral and psychological strategies or variables. The types of interventions that have proven efficacious to some degree within research paradigms are listed in Table 1.

INTERVENTIONS TO REDUCE POSTSURGICAL AND OTHER ACUTE PAIN

Information Provision

It is common for patients to experience significant levels of fear and anxiety about any medical procedure. With major surgery or invasive procedures, patients express fears of anesthesia, fears of experiencing pain, and fears of complications, even death. In addition, anxiety can accompany postsurgical pain, especially when that pain is interpreted as a signal of physical malfunction or abnormality rather than as normal pain or tenderness. Because the presence of fear and anxiety is strongly related to increased pain levels, methods of reducing anxiety about surgery have been targeted as a means of reducing pain experience as well.

The provision of information about an upcoming surgical procedure has been widely explored as a means of reducing postoperative pain levels. Providing accurate information to patients is thought to reduce anxiety by establishing reasonable expectations about the sequence of events and sensations, thus reducing fear and worry resulting from experiences that are unfamiliar or unanticipated. The reduction of anxiety theoretically then reduces, or at least minimizes, pain experience. Information provision has been separated into three types: procedural, sensory, and temporal.

Procedural, Sensory, and Temporal Information. Egbert et al[8, 9] were the first to report that a preoperative informational visit by the anesthetist had highly favorable effects on postsurgical pain levels, narcotic use, and length of hospital stay. Egbert and other investigators provided what is termed "procedural information,"—relating specific information about the sequence of events to expect before, during, and after surgery.[20, 21] Other studies have looked at the effects of sensory information.[16–18] In the provision of sensory information, the patient is told ahead of time what postoperative sensations may be expected. These are given in descriptive terms other than "pain;" for example, stitches pulling, bloating of abdomen, and stinging.[18] This intervention is also used widely in clinical preparation for painful medical procedures such as bone marrow aspirations, in which patients are told what sensations to expect (such as pricking, pressure, and so forth) and when during the procedure to expect them.[14] Temporal information has been effectively added to the sensory information so that patients know when, for how long, and how frequently events are likely to occur.[16]

Coping Style Influence on Information Effects. Although several studies have shown increased pain tolerance, decreased analgesic use and faster recovery with procedural, sensory, and temporal information either alone or in combination,[16–18, 28] others have yielded inconclusive or equivocal results.[31] Therefore, it is difficult to state definitively whether information provision alone is truly effective in reducing postoperative or procedural pain and distress. It does seem clear that sensory and temporal information are more effective in reducing pain than procedural information alone. It may be, however, that the effects of another variable, patient coping style, have confounded these studies.

A fair amount of evidence suggests that the effects of information provision may be moderated by a patient's individual coping style. Probably the most researched coping styles have focused on contrasting avoiders/repressors and sensitizers/copers. Avoiders or repressors are described as people who seek to avoid information or cognitions about stressful situations and thereby contain their anxiety. They may minimize distressing information provided or may insist that everything will be fine. Sensitizers or copers are described as more actively seeking information and more likely to express anxiety by seeking reassurance. This dichotomy is simplistic, of course; in fact, a number of coping strategies may be subsumed under these coping styles.[6] For example, sensitizers may be action oriented and want to know exactly what they can do about a problem; alternatively, they may be openly fearful and seeking of support from others to cope with their anxiety. In studies investigating information provision and coping style, some evidence has shown that avoiders, people who tend to avoid or repress anxiety in stressful situations, may experience more pain and anxiety with increased information.[1, 6] At the very least, it seems that they may gain no benefit from presurgical information provision.[38] Scott and Clum[26] investigated these coping styles and concluded that information provision had no beneficial effect for sensitizers without the addition of coping skills training; in contrast, avoiders tended to do best when left alone. Johnson and colleagues[18] found that information was most helpful when combined with instruction in deep breathing, movements to reduce pain, and exercises to assist recovery.

Information Provision Conclusions. Although the evidence is not yet conclusive regarding the benefits of informational approaches, it seems clear that the effects of information provision are not as uncomplicated as they first appear. Rather, patient characteristics modify the effects of information. For some patients, it is not enough to discuss what will happen and how it will feel. This information can be used best when combined with training or instruction in behaviors or exercises that can minimize discomfort. For other patients, limited information is most desirable, and the details required for informed consent may be more than sufficient for their preferences.

These conclusions strongly suggest that supportive contact be made preoperatively, and that the clinician needs to be sensitive to the anxiety level of the patient and the response of the patient to information. Typically, patients who are concerned about possible pain or are extremely anxious may benefit both from increased information and perhaps from referral for training in coping skills (see following discussion). These strategies can increase their sense of perceived control and relieve anxiety. On the other hand, if patients do not ask questions or if they seem unconcerned about details that are potentially distressing, they may not benefit from blanket, unsolicited information provision. Obviously, sensitive observation and assessment is the key.

It must be noted that research on information provision with children is even more scarce than that with adults. Information has been a component of the Cognitive Behavior Therapy Package offered to children by Jay, Elliott and colleagues.[15] As with adults, information is likely to be most effective when combined with coping interventions and with attention to the style of the patient.

Cognitive Coping Strategies

The term "cognitive coping strategies" covers a fairly broad range that typically includes (1) interventions to change cognitive appraisal of the situation and (2) interventions that focus on the cognitive transformation of sensation or the use of imagery and other distractions to divert attention away from pain.

Appraisal. Cognitive appraisal refers to the thoughts or beliefs patients may have about the meaning of an event or about their ability to cope with an anticipated experience. The use of coping self-statements is a method that targets cognitive appraisal of a situation.[30, 34] Changing self-statements is based on the assumption that patients' cognitions in stressful or painful situations may be unrealistic, catastrophizing, and anxiety-enhancing. For example, if a postsurgical patient appraises his or her pain as "abnormal" and worries about whether the surgery was truly successful, anxiety and pain levels are likely to be focused on and increased.

Therefore, this strategy attempts to define the patient's areas of anxiety and then teach calming "self-talk" designed to enhance active coping and a sense of self-efficacy. An example might be a patient anticipating surgery who is thinking "the pain could be unbearable; what if I can't stand it?" Calming self-talk might substitute "it's normal to be sore and tender after surgery; I can always practice my deep breathing or ask for medication." The goal of this self-talk is to redirect the mind away from disturbing thoughts and then to institute actions that increase patient control and, if possible, decrease pain experience.

Self-statements have been used extensively with chronic pain patients, but few acute pain studies have specifically looked at their impact. However, stress inoculation programs for acute pain have routinely included self-statements embedded in a variety of other coping methods.[19, 35]

Attention Versus Distraction. Attentional strategies and imagery have been more widely investigated within laboratory analogue pain studies than in clinical settings. These techniques are focused directly on pain control rather than on reducing associated fear or anxiety. These methods include a wide variety of attention, distraction, and transformation strategies. For example, patients can be taught to imagine relaxing or absorbing situations that are incompatible with pain (for example, the beach). It is also possible to mentally transform the pain by imagining the area to be numb, cold, or anesthetized, often using conjunctive imagery, for example, of ice cubes on the area. Mental distraction can be helpful for focusing attention away from the pain and onto any mental task that requires attention and thought. The patient can focus on some other physical characteristic of the environment or on cognitive activities such as mental arithmetic, reciting poetry, or singing.

Many of these attentional methods of pain control have been investigated via laboratory analogue research and have produced hopeful if not unequivocal results. With clinical acute pain, however, the relative efficacy of distraction versus attention may be more complex. In an extensive review of the distraction literature, McCaul and Malott[22] propose that distraction is most effective when the strategies used are more engrossing. For example, imagining reclining on a beach or counting would be less distracting than imagining participation in an activity that aroused emotion such as dancing or even fighting.

McCaul and Malott also determined that distraction is most effective for lower intensity pain. As pain intensity becomes severe or as time passes, distraction becomes less effective and attention to or "redefinition" of the pain becomes more effective. With this strategy, the patient is instructed to attend to and monitor sensation in an effectively neutral manner, reporting on the experience. Whether this strategy is effective because the emotional component of the pain experience is reduced or because this becomes a form of sensation transformation is not clear. Our clinical experience suggests that when pain is severe, extends into days or weeks, and requires opioid analgesics, patients have difficulty sustaining the energy and concentration required for distracting imagery or thought. At this point, attentional monitoring may be more helpful but less enjoyable for patients than strategies involving escape through distraction. As a result, this method tends to hold less appeal. Further work is needed into methods of training patients in redefinition of pain through attention.

Overall, research investigating the efficacy of these strategies both in analogue and clinical pain studies has not produced definitive results.[22, 23] These results may vary in part because many people spontaneously use cognitive strategies of their own devising to cope with pain.[25] Additionally, as commented on by Turk and colleagues,[34] the patient's assessment of his or her ability to use the coping skills at hand determines to a large extent actual success in using these strategies. Therefore, the patient's sense of self-efficacy and confidence in being able to cope with stressful or painful events is a crucial factor. Our clinical experience also suggests that some patients are less able or interested in mobilizing their imagination actively for this purpose than are others.

It may be that the cognitive coping strategy actually used is no more important to the outcome than is the patient's confidence that he or she has coping skills that are usable. This underscores the need for individual assessment and points toward the stress inoculation model in the following discussion for enhancing patient sense of perceived control.

Relaxation Training and Related Techniques

Deep Breathing. Deep breathing techniques, progressive and passive muscle relaxation training, or hypnotic procedures have been incorporated into most acute pain management programs. Deep breathing typically involves teaching patients how to breathe in a controlled and structured manner to slow autonomic arousal and reduce feelings of anxiety.[5] In clinical settings most health care professionals are aware of the benefits of deep breathing. We have found that it is usually not sufficient to simply tell anxious patients in pain to take deep breaths. Rather, it is most beneficial to instruct patients (preferably before the painful situation) in a structured deep breathing technique that includes both holding the inhalation for several seconds and slow complete exhalation. If simply told to take deep breaths most patients continue to breathe fast; therefore, breathing more deeply can increase anxiety and the likelihood of hyperventilation. A good guide to deep breathing is found in the workbook by Davis, Eshelman, and McKay.[7]

Muscle Relaxation. Muscle relaxation training (which typically involves either tensing and relaxing or simply focusing on and relaxing muscle groups) has been widely investigated in the psychological literature and found very effective in reducing anxiety and muscle tension.[4] Muscle relaxation has also been shown to be effective in reducing pain by studies investigating both postoperative and acute laboratory pain.[11, 26] Often, imagery or hypnotic techniques incorporate muscle relaxation instructions to facilitate physical relaxation and suggestibility.

Hypnosis and Imagery. There are many laboratory and clinical case reports investigating hypnosis and its effects on pain control. The controlled clinical trials literature on hypnosis for pain control is quite small but has shown some success.[27, 29] Although relaxation and deep breathing can be assumed to reduce pain primarily via their anxiolytic effects, hypnosis has been hypothesized to reduce pain via additional mechanisms such as attentional control or dissociation[12] and may be, for some people, more effective than relaxation alone.

Hypnotic strategies usually include a process similar to that used in relaxation and imagery. First, attention is captured through deep breathing, closing the eyes or focusing the eyes on another activity. Next, relaxation or a similar induction directs attentions away from pain, enhances relaxation, and reduces arousal. Finally, imagery is incorporated to further absorb attention and transform sensation, mentally removing the patient from the painful situation. Suggestions are combined with imagery for enhancing feelings of well-being, comfort, and control.

Patients vary in their initial response to this procedure depending on their hypnotizability. Although highly hypnotizable patients may respond with greater reduction of pain, with practice it seems to us that any motivated patient can benefit from learning to use these techniques to increase comfort. Our clinical experience also suggests that hypnosis is effective for acute pain largely through a mechanism of attention redirection. In some cases hypnosis may capture and hold a patient's attention more effectively than other forms of distraction and, as a result, will be more effective for acute pain than relaxation without imagery. For more susceptible patients, hypnotic suggestion will extend inattention to pain for several hours or days after the induction is complete.[3, 12]

For all hypnosis or relaxation-associated strategies, success in pain reduction appears to be achievable consistently only when patients have had sufficient practice so as to truly acquire the skill.[10, 24] For example, patients who are simply given audiotapes are rarely able to use the techniques successfully. The relaxation literature consistently supports the need for individual training and follow-up if benefits are to be obtained from these methods. If a clinician determines that hypnosis or relaxation might be effective for a patient, we recommend a referral to an experienced therapist.

Increasing Perceived Control

Control or perceived control over aversive or painful events is widely known to decrease the reported pain or aversiveness of those events.[2, 33] Although all of the psychological strategies discussed previously essentially help to enhance the patient's sense of control, none of them are aimed specifically at that target. Instead these techniques have typically been approached on a skills-acquisition, nomothetic basis. Taylor[32] suggests that excessive pain behaviors within the hospital setting, as well as general "bad patient" behaviors can be attributed to loss of freedom and control typically found in hospitals. A hospital setting, by its very nature, involves a number of factors that reduce patients' sense of control and tend to increase anxiety. These factors include physical malfunction, threat of invasive treatments, fears of disability or death, loss of normal routine and comfort, and loss of privacy and identity. Taylor,[32] Peck,[24] and others have advocated for an approach to pain control that emphasizes the patient's sense of efficacy and perceived control.

Stress Inoculation. One psychological management strategy that addresses the issue of patient control more directly is the stress inoculation approach.[34] This model incorporates a wide range of available techniques or options and allows the patient freedom to choose a preferred approach, thus enhancing pre-existing skills and increasing choices. Stress inoculation has three phases. The first phase is simple education in the gate-control theory of pain.[23] The second phase consists of presentation and rehearsal of a wide variety of cognitive-behavioral techniques (for example, relaxation training, imagery, distraction, calming self-statements). In the third phase, patients are encouraged to choose one or more of these techniques and practice them within simulation of the anticipated experience. This rehearsal of coping with the painful event may be a key element. This process has been shown in two well-controlled experiments to be effective, first with burn patients during the acute pain of debridement,[36] and most recently in reducing postsurgical pain.[35] Peck[24] points out that in implementing these methods it is critical to provide a sufficient amount of time for preparation, training, and practice of the techniques for maximum efficacy.

Patient-Controlled Analgesia. Another area in which patients can benefit from increased perceived control is with respect to administration of analgesic medications. There is some evidence that postsurgical patients may be routinely undermedicated even when narcotic analgesics are prescribed for them.[6] Although early reports on the use of patient-controlled analgesia (PCA) apparatus were mixed, the method is now widely used in postoperative settings with positive results.[37] Recently, it has been demonstrated that bone marrow transplant patients using PCA pumps for up to 3 weeks for oral mucositis pain following chemotherapy and irradiation continued over the entire pain course to use significantly less narcotic than did patients receiving continuous infusion administration.[13] In clinical experience with oral mucositis pain, some patients clearly prefer not to have direct control, via PCA, over their opioid intake. Therefore, having a choice of analgesic administration method may be of great importance in optimizing feelings of perceived control in an acute pain setting. It may be that patients with high self-efficacy prefer to be in control of their own medication while those with lower self-efficacy in medical settings experience more control when they feel the doctor or nurse is in charge.

Intruction in Self-Care Activities The third potential area for increasing perceived control lies in self-care and activity. Some of the literature on information provision has investigated the provision of instructional information that teaches patients how to move, cough, or do other self-care activities that can decrease their pain-related difficulties. Johnson et al[16, 18] found that instructional information led to decreased analgesic medication use and increased postoperative activity. Increasing personal control by having patients participate in their own care, and by encouraging them to view activity as positive in spite of pain, may be as helpful in reducing the reported pain and distress of acutely ill patients as it has been in increasing the adaptive functioning of chronic pain patients.

SUMMARY AND GUIDELINES FOR MEDICAL APPLICATIONS OF PSYCHOLOGICAL STRATEGIES

In summary, the key issue in psychological approaches to acute pain management seems to lie in the ability of patients to experience a sense of personal control and efficacy in their pain management and indeed in their overall medical care. Although many techniques can be useful in achieving this goal, in the end patients choose what will and will not be helpful to them. Therefore, we offer the following guidelines to acute pain management in medical settings.

1. Conduct preprocedural or preoperative assessments, screening for level of anxiety and information-seeking, desirable method of postoperative pain control, and willingness to accept coping skill training.
2. Provide procedural, sensory, and temporal information to patients who clearly desire information or are anxious about an upcoming procedure.
3. Refer patients who are anxious or having difficulty with pain management or compliance with pain treatment to psychosocial resources for training in coping techniques. Provide choices of preferred coping strategies wherever possible. Strategies available include relaxation, hypnosis, cognitive techniques, distraction, and enhancing perceived control. Allow enough time for patients to acquire the skills.
4. Provide instructional information in regard to activity postsurgically. Training in movement and levels of activity has been shown unequivocally to be helpful in convalescence.
5. Whenever possible, provide patients with choices and options to enhance their own sense of control. For some patients this may mean that they exercise more self-care options; for others it may mean that they are choosing for the health-care provider to take charge.

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Psychological Issues in Postoperative Pain

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An observation frequently made in treating postoperative pain is the variability in patient response to the same type of surgery and a medically similar postoperative course. For any given surgical lesion, there are differing magnitudes of pain complaints and analgesic requirements. One explanation for this range of response is that the right pharmacologic key has not yet been discovered for the patient complaining of severe, postoperative pain. An alternative possibility is that psychological factors may be contributing significantly to the amount of pain perceived and expressed. Research in the acute pain literature suggests that psychological factors do play a role in exacerbating or minimizing the pain response of the postoperative patient; these include fear and anxiety, sense of loss of control, isolation and separation from normal social supports, learning of cultural and familial responses to pain, and the individual's prior experiences with pain and suffering.

Pain is a very complex phenomenon; it has been said that one may wonder about or even question the pain another person reports experiencing, but one never doubts its existence in oneself. Pain is, thus, a private experience; it is not directly measurable and its presence can only be indirectly assessed by patient report or by the judgment of others who observe the patient's behavior. In this sense, pain is like an emotion. The emotion of anger, for example, cannot be seen but is assumed to be present when an individual acts in specific ways (for example, slamming doors, cursing) especially when circumstances lead the observer to believe that anger might be an expected emotional response (for example, when the person has been unfairly treated). In the case of pain, its presence is assumed when known circumstances suggest pain might be present (post surgery) and when the person is observed to behave in ways that suggest a noxious stimulus is being experienced (verbalized complaints of pain, crying out). Even when pain is assumed to be present, the patient's style of expressing it can also be highly variable. There are those individuals who appear unwilling to acknowledge pain from a major injury, possibly because of a very high "pain tolerance" or because of a coping style that finds expression of any pain unacceptable.

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These contradictions and complexities raise many questions about the nature of pain itself, and the perception of pain. This article is written to provide anesthesiologists and other pain management team members with a different way to conceptualize what is clinically observed.

THE NATURE OF PAIN

The concept of pain is further complicated by confusion over what is actually being measured; there has been in the past the assumption of a direct connection between the complaint of pain and underlying nociception. Nociception has been defined by Loeser[11] as the "detection of tissue damage by transducers in skin and deeper structures and the central propagation of this information via A delta and C fibers in the peripheral nerves." Pain is the recognition of nociceptive stimulation by the central nervous system; pain can also be recognized when an injury to the peripheral or central nervous system has occurred (deafferentation or central pains). There is, however, no simple, direct relationship between nociception and pain complaints. There can be nociception without evidence of the individual experiencing pain, and there can be a pain response without nociception. The amount of pain about which the patient complains, whether verbally or nonverbally, thus is not necessarily an accurate reflection of underlying nociception; for example, Bonica and Benedetti[2] determined that 30 per cent of those undergoing major surgery report only mild pain and require no postoperative analgesics. On the other hand, anesthesiologists managing postoperative pain see many individuals with the same lesions as others requiring significantly greater amounts of analgesic medications than predicted. Wide individual differences in response to surgery challenge the finest technology to adequately manage their suffering.

ACUTE VERSUS POSTOPERATIVE PAIN

The term "acute pain" is often used interchangeably with "postoperative pain" as if they are one and the same. In reality, postoperative pain forms a circumscribed area within the larger context of acute pain, and, as such, has its own specific situational features with unique concomitant psychological responses. Although from a strictly physiological perspective, the tissue damage from an acute traumatic injury may be very similar to that incurred during a surgical procedure, these are very different events from the patient's point of view. A patient who has undergone a routinely scheduled thoracotomy is having a very different hospitalization experience than is the individual who was brought by ambulance into the emergency room after having been slit with a knife during a mugging. Situational variables surrounding the "cause" of the pain, whether trauma or surgically induced, will have a differential impact on the patient's affective and behavioral responses to the pain that he or she perceives.

Even acute, trauma-induced pain requires finer distinctions to be made prior to being able to address psychological factors that contribute to, or emanate from the noxious stimulus. Clearly, the degree of severity of injury, whether postoperative or trauma-induced, has an impact on the affective, or emotional, response. Expected as well as actual time course of the pain is a significant factor in determining the individual's response on a psychological level and, quite likely, on a physiological level. A painful input that lasts 30 seconds, one that persists for 3 days, or one that continues for 3 weeks, will certainly have different effects on the individual anticipating and experiencing it. Research that fails to make the distinction of severity, time course, or major situational variables such as postoperative or trauma-induced, will have little generalizability or usefulness in clinical applied settings.

CHRONIC AND POSTOPERATIVE PAIN

The distinction between chronic pain and postoperative pain is a very clear one, and there may be only a weak relationship between factors contributing to chronic pain states and factors contributing to postoperative pain. A pain problem that exists for years bears little resemblance to the typical postoperative course of gradually diminishing pain over a matter of days. The contribution of the extensive literature on chronic pain to the field of postoperative pain lies primarily in the heuristic value of generating hypotheses to be tested in the postoperative setting. Specifically, from the chronic pain literature, comes pain assessment techniques; the use of psychological interventions that work in conjunction with pharmacology and procedures; an established vocabulary to describe and characterize pain; and, especially relevant to this article, the working hypothesis that psychological factors may play a role in the exacerbation of the postoperative pain experience. In contrast to the field of chronic pain, there has been little research or clinical attention paid to psychological contributors to postoperative pain.

Pain has been understood to be the consequence of invasive surgical techniques, and efforts in postoperative pain management have been focused on developing technology, both procedural and pharmacologic, for managing as much of the pain as possible, while minimizing adverse side effects. Aggressive postsurgical pain management, particularly with the arsenal of techniques and pharmacology available in larger medical centers, has been very successful in relieving pain and smoothing the postoperative course of many patients. Until very recently, there has been little impetus to address the psychological factors that are inherent in the surgical and postsurgical experience.

In chronic pain management, the incentive to pursue psychological factors came from frustration over the failure of the conventional medical approach to restore a subset of individuals to the expected level of functioning given their physical findings. In the postoperative setting, the majority of patients do not present significant management problems; as noted earlier, however, some do challenge the best efforts at managing their pain. At the current level of postsurgical pain management, even when sophisticated and effective analgesic procedures are applied in a technically flawless fashion, some patients still fail to get adequate pain relief. In addition, it is becoming increasingly apparent that the surgical and postsurgical experience is a tremendous psychological stressor to virtually all patients, requiring mobilization of all of their emotional resources in order to cope with what may well be the most distressing experience of their lives. It is possible for physicians and other medical personnel to overlook the significance of both the surgery and the postoperative pain in patients who are relatively unfamiliar to them and with whom they know they are going to have a limited period of contact; comprehensive postoperative pain management, however, dictates an approach that includes consideration of psychological, as well as physiologic, issues.

PAIN BEHAVIORS

In the process of doing clinical and research work with chronic pain patients, the term "pain behaviors" was developed to describe that which an individual does or does not do, says or does not say, which leads an observer to infer that the person is experiencing a noxious stimulus.[9] It says nothing about the etiology, chronicity, or legitimacy of the pain.

The use of the concept of "pain behavior" has allowed some measure of objectivity to enter into the pain equation as behaviors are, by definition, observable and quantifiable. The number of times a patient requests narcotics, the amount of splinting, the verbal response a patient gives to an inquiry about the level of pain he or she is experiencing are all examples of potentially quantifiable pain behaviors and provide guidance to clinicians and researchers as to the exacerbation or reduction of pain levels. Elaborate observational schemes for measuring and quantifying pain behaviors have been developed specifically for use with chronic pain problems[10] but, even within the postoperative setting, patient use of narcotics, general level of functioning, and activity level have been used informally to guide staff in assessing ongoing pain levels. Unfortunately, the use of the term "pain behaviors" so extensively in the chronic pain literature has resulted in its having a pejorative meaning when, in actuality, it is merely a descriptor of an observed action.

Pain behavior has come to mean, to some clinicians and researchers, that the etiology of the pain is in question, that it might not be "real" or that the patient is deliberately engaging in such behaviors for a specific purpose. An individual who has just had his leg crushed in a car accident and who is conscious and nearly overwhelmed by nociceptive input is almost certainly going to engage in "pain behaviors," such as crying out, moaning, or writhing. While pain behaviors communicate to an observer that the individual is experiencing pain, this is by no means necessarily a conscious attempt to communicate, any more than tears at a funeral are intended to communicate sadness. Nonverbal behaviors communicate something whether or not the individual intends it. Because pain behaviors are the only clue the observer has to the presence or level of pain experienced, the term will be used in this article and seems likely to make its way into postoperative research in the future to a greater extent.

FACTORS INFLUENCING POSTOPERATIVE PAIN RESPONSE

If there is not a direct connection between nociception, pain, and pain behaviors, what nonphysiologic variables might be intervening between the detection of tissue damage, pain perception, and behavioral response? Although a number of explanatory theories have been proposed to explain the frequent discrepancy between input (nociception) and output (pain behavior), two general factors appear to be the most useful in terms of explaining the wide range of individual differences, and even the variation within the same individual, at different times and under different circumstances. These factors are learning and suffering.

Learning

The learning model, which has proved so useful in the arena of chronic pain, postulates that behavior is the result of prior and current learning experiences. Behavior is responsive to environmental consequences; that which is followed by positive consequences tends to be repeated and that behavior which is punished or ignored tends to decrease in frequency. Learning can occur by consequences one experiences oneself, or by observing others' behavior and its resultant consequences.[9] An individual's behavior is profoundly influenced by early lessons within the family. All children have episodes in which they are sick or injured; family responses are extremely varied, with one family focusing attention, nurturing, and solicitousness on a child while another family ignores the illness or injury and makes it clear to the child that admiration and respect of the family are contingent on stoicism. Children also observe the behavior of important others when they are in pain and thus, learn the acceptable familial response to pain.[6] These are powerful lessons often carried unchanged throughout life and certainly account for some of the behavioral variation seen between patients postsurgically.

Learning, however, is not static; individuals continue to be influenced by environmental consequences of their behavior. In the postoperative period, the response of staff and family has an influence on the degree and frequency of pain behavior or complaints. Several studies have shown that contingent attention and reinforcement can cause increases in pain behaviors.[8, 9] When a solicitous spouse is present, the patient's pain ratings have been shown to be consistently higher than when a neutral person is present.[1] While virtually all of this research has been conducted with chronic pain patients, anyone who has worked closely with patients in the acute or postoperative setting has observed changes in a patient's demeanor with respect to pain and suffering when certain family members or friends are present. Individuals sharing a hospital room with other patients in the postoperative phase may also be influenced by the roommate's pain behaviors and staff responses to them.

If a patient who is experiencing severe anxiety while awaiting a pathology report complains of the pain he or she is also experiencing, the nurse may respond with an increase in the administration of opioids. Since a side effect of a pain medication such as morphine can be a decrease in anxiety, the likelihood of the pain behavior or complaint occurring the next time anxiety becomes overwhelming is greatly increased. Similarly, the patient who is frightened of the hospital environment and does not want to be left alone will often find that complaining of severe pain leads to family members staying close by. Both prior learning about how one should respond to pain and current consequences of pain behaviors are likely to have a significant impact on the postoperative patient's ways of coping and communicating the experience of pain to hospital staff.

Suffering

The concept of suffering is another contribution from the field of chronic pain that is highly relevant to the postoperative setting. Suffering can be conceived of as the result of the patient's cognitive appraisal of the total situation surrounding the surgery and the reason for it. Pain for the postsurgical patient is a continuous reminder of the surgical experience and all the hopes and fears associated with it. Suffering is defined here as a negative affective response, the sum of all of the negative connotations surrounding the way in which the individual appraises the pain. Anxiety and fear form a substantial part of suffering in the acute or postoperative phase, whereas depression may play a larger role once the pain has been experienced over a prolonged period.

Fear and Anxiety. Fear related to a specific threat or pervasive general anxiety are the major emotions associated with acute pain and, in particular, with postoperative pain. Virtually all surgeries and, certainly, all major operations, confront the patient with the possibility of death. Fear of death gives rise to the most intense levels of distress individuals are likely to experience. Once the patient has survived the surgery, the fear of dying on the operating table is often replaced by general anxiety about bodily well being, body integrity, altered functioning, life changes and, in specific instances, continued fear about death, the results of the pathology report, and often, profound fear about pain.

A survey conducted by the author on 50 postoperative patients, 2 days after surgery, found that levels of fear and anxiety were described by patients as being higher than their current levels of pain, although the two tended to be highly correlated.[7] Even when attempts are made to prepare patients for surgery and to support them emotionally during their postoperative course, patients are likely to be highly anxious. Fear of the unknown, fear of loss of control, and fear of anticipated medical procedures were the most frequently mentioned sources of anxiety by the patients participating in the survey. Ironically, the sophisticated technological machinery used in critical care and intermediate care units to manage pain and to accurately monitor bodily functions contributes significantly to patient fears. In the author's survey the patients who were intubated and whose lives were maintained by complex and frightening equipment were the most fearful of all patients. In addition to being artificially ventilated by a machine that could conceivably break down, such patients, because of the presence of an endotrachial tube, are unable to communicate verbally with others. Many of the electronic aids, thus, serve to isolate the postoperative patient from usual sources of comfort and contribute to the patient's fears. Anxiety has been shown to have a strong relationship with level of pain reported in a number of studies in the area of postoperative pain.[3–5, 12, 14–16] Studies show a linear relationship between anxiety and pain, with higher levels of pain associated with increased anxiety. When anxiety, fear, and apprehension become more pronounced, not only do reported pain levels rise, but the patient tends to request more narcotics in the postoperative period.[15] It may well be that patients are treating their anxiety and distress with pain medications.

While pain and anxiety are highly correlated, it cannot be determined, based on current research, whether it is the anxiety that increases pain perception or whether higher levels of perceived pain cause increased anxiety; pain and anxiety are conceptualized as contributing to each other in a complex, poorly understood fashion.[5] While pain itself clearly produces anxiety, psychological factors by themselves appear to impact nociception, the detection of tissue damage, and thus, influence the amount of perceived pain. Zimmerman has noted that sympathetic activity, which can be generated by such psychological states as anxiety, affects the microcirculation of the tissue environment of the nociceptors as well as the chemical environment.[18] Thus, the release of epinephrine at sympathetic endings may sensitize or actually activate nociceptors.[4] Intervention studies in the pain literature have targeted anxiety as causing increased pain; successful treatment of anxiety has been related to decreased pain complaints and increased functioning on the part of individuals experiencing acute pain.[4, 14, 17]

Cognitive Appraisal: The Meaning of the Pain. While anxiety and fear play a major role in the patient's degree of suffering, their presence is often not the result of the immediate hospital environment alone. Particularly in the postoperative patient, the generalized distress is a function of the significance of the surgery in the patient's life. The same surgery performed on two different patients for different reasons is likely to result in each patient appraising or evaluating the resultant pain quite differently. The woman recovering from plastic surgery to rebuild her face after a severe burn and the woman who chooses to have similar surgery to improve her facial features and enhance her attractiveness, would not be expected to regard surgery (and its accompanying pain or discomfort) in the same way. Hysterectomy for painful fibroid cysts in a woman who does not wish to have children and hysterectomy for invasive, metastatic carcinoma is likely to result in very different postsurgical responses in the patients.

In the examples cited, the distinction drawn is in the "meaning" of the pain to the patient. It is impossible for the patient to separate the actual situation leading to the surgical procedure as well as the perceived outcome of the surgery from his or her experience of the pain. The pain serves as a potent reminder, after surgery, of the circumstances surrounding its etiology. The author had the experience, when first working as a consultant on a surgical unit, of being asked to see a woman who had undergone exploratory abdominal surgery to determine the cause of a nagging, low-level, but continuous pain; the surgeons were very surprised to find an inoperable recurrence of a malignancy. The woman had been considered "cured" as it had been 10 years since her original malignancy. It became clear in talking to her that the surgeons had not yet informed her of their findings. The patient was lying comfortably in bed discussing her son's upcoming wedding and not spontaneously complaining of pain. When asked, she rated the pain a "1" on a 10 point scale. After the consultation team left, the surgeons came in and told her the results of the surgery; the consultation team returned within 15 minutes of the surgeons' departure to find a dramatic change had occurred in the woman. She was then writhing in bed, holding her abdomen and crying, "The pain!, the pain! I can't stand the pain. Give me something for the pain!" It seems unlikely that the actual nociceptive input had changed in the 15 minutes that had elapsed between the two visits. What *had* changed was the meaning of the pain, the degree of suffering, and her response to the pain. Patients and physicians alike often use the language of pain to describe suffering of any etiology; in requesting "something for the pain," the patient was seeking to diminish her intolerable suffering.

While the use of narcotics to treat acute suffering can certainly be a legitimate use, it is important for staff, working with postoperative patients, to be aware that suffering is often expressed as pain by the patient; if the assumption is made that noxious physiological stimulation is the problem to be treated, the patient can be done a serious disservice. Unnecessary and potentially harmful diagnostic tests and surgeries may be pursued and ever increasing doses of pain-relieving (and mind-obliterating) drugs may be prescribed when what the patient really needs is a listening ear and a clear mind to begin to address the real issues that may be easier to escape from pharmacologically initially, but that ultimately require a different, nonmedical approach. In the attempt to treat the "pain", the patient reports, the suffering may actually be made worse.

A major clinical challenge for those charged with managing postoperative pain lies in maximizing pain relief while minimizing undesirable side effects. Assessing pain levels and analgesic needs requires an awareness of the many variables that influence the expression of pain; these include, in addition to nociceptive input, the patient's appraisal of the total operative experience, the dangers and losses associated with it, fear and anxiety, as well as the patient's learned style of coping with pain and illness. "Minimizing undesirable side effects" is not limited to reducing unwanted physical side effects such as nausea or urinary retention. There are undesirable side effects associated also with physicians being so focused on the nociceptive aspects of pain that that patient fails to receive optimal management of both the pain and the concomitant suffering. Research, thus far, into the psychological factors surrounding postoperative pain, is in its infancy, but as technology advances, the questions arise and research emerges from clinical experiences. It is hoped that the research will eventually make a useful contribution to the confidence and awareness of those who have to manage the very complex phenomena of postoperative pain.

SUMMARY

Psychological issues that impact on postoperative pain are beginning to receive theoretical and research attention. Psychological factors are likely to contribute significantly to the wide range of individual variation in response to standard surgical interventions. Pain is a private, internal experience; its presence can only be inferred by observations of patient behaviors, both verbal and nonverbal. Postoperative pain is a unique category of acute pain and, as such, requires an approach that considers the psychological factors relevant to the surgical and immediate postsurgical experience. Nociception, or detection of tissue damage, does not explain the extent of pain complaints in different patients, and in the same patient at different times. Psychological factors that intervene between nociception (surgical lesion) and pain behaviors (requests for narcotics, nonverbal expressions of pain, pain ratings) can be generally summarized as those that have to do with learning (prior and present) and those that have to do with the amount of suffering the individual is experiencing. Suffering includes all the negative emotions associated with the pain itself, the hospital experience, resultant fear and anxiety, and the patient's appraisal of the "meaning" of the surgery and subsequent pain. Awareness of these issues can prevent well-meaning, but potentially dam-

aging medical procedures and escalating drug doses that can actually contribute to, rather than diminish, the patient's suffering.

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Opioid-Induced Respiratory Depression in the Postoperative Period

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This article examines the problem of opioid-related respiratory depression, particularly in the postoperative patient. Dissatisfaction with intramuscular or intravenous pulse injection of opioids has led to the development of alternative routes and techniques of administration.[32, 95] These include continuous low-dose intravenous infusions of opioids, patient-controlled analgesia (PCA), and spinal administration of opioids (epidural, intrathecal) either by pulse injection or continuous infusion. In general these newer techniques of administering opioids are very effective in controlling postoperative pain, but there are few controlled studies comparing the analgesic or respiratory depressant effects of opioids when administered by these different techniques.[94]

HISTORICAL PERSPECTIVE

The fact that opioid analgesics, pain relief, and respiratory depression are related intimately has been known for centuries.[44] Since 1941 when Krueger et al[53] compiled an exhaustive document on opioid analgesics, there have been numerous reviews at regular intervals on drug-induced respiratory depression including the effects of opioids on respiration.[11, 12, 15, 16, 18, 36, 44, 49, 50, 55, 65, 72, 76, 93, 98] These extensive reviews illustrate that most of the investigation on opioids and respiratory depression has been performed on healthy volunteers, preoperative patients, or patients undergoing anesthesia. Very little attention has been paid to postoperative patients in spite of the fact that opioids form the mainstay of postoperative analgesia.

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RESPIRATORY DEPRESSION

From a pathophysiologic point of view, respiration is depressed if the subject fails to respond adequately, on a moment-to-moment basis, to hypercapnia or hypoxia.[73]

Detection and Measurement

The detection and measurement of drug-induced respiratory depression is reviewed by Jordan.[48] Methods currently available are summarized in Table 1.

Indirect Measurement

In the clinical setting it is most common to measure the respiratory rate intermittently. Although this is clearly the simplest form of monitoring, it has serious shortcomings in that the technique does not detect transient events. In addition, the relationship between respiratory rate, hypercarbia, and hypoxia is unreliable. In particular, patients may be hypoxic and hypercapnic yet have a normal respiratory rate.[21, 83, 92, 99]

Respiratory inductance plethysmography (RIP), in which two zigzag coils of wire are placed around the chest and abdomen, gives a semiquantitative measurement of ventilation that is relatively insensitive to changes in posture. The device is comfortable and well suited

Table 1. *Methods of Detection and Measurement of Respiratory Depression*

I. Measurement of resting breathing
  A. Ventilation
    1. Direct
      a. Spirometry
      b. Pneumotachograph
    2. Indirect
      a. Canopy
      b. Strain gauge
      c. Respiratory inductive plethysmography
  B. Blood gas tensions
    1. Direct
      a. Arterial blood gases
    2. Indirect
      a. Transcutaneous Po_2 or PCo_2
      b. End-tidal Co_2
      c. Oximetry
II. Tests of chemosensitivity
  A. Response to Hypercapnea
    1. Co_2 response curve
    2. Mouth occlusion pressure
  B. Response to hypoxia
III. Measurement of response to added mechanical load

Adapted from Jordan C: Assessment of the effects of drugs on respiration. Br J Anaesth 54:763, 1982.

for continuous monitoring. It allows the observer to discriminate between obstructive and central apneas and detect paradoxical respiratory movements. However, this technique does not detect hypoxia or hypercapnia directly.[20, 24, 28, 40, 48, 100]

The best indirect measurement of PaO_2 is obtained with the pulse oximeter. Oximeters are generally accurate at saturations above 70 per cent, have a rapid response time, and are comfortable for long-term monitoring.[17, 75] In the presence of supplemental oxygen, however, saturation may be well maintained despite significant hypoventilation or apneic episodes.[47]

Direct Measurement

Altered chemosensitivity, in particular the depression of the CO_2 response curve, is considered a sensitive index of respiratory depression.[48, 73, 76] Because there is significant between-subject variability, it is important that subjects serve as their own controls. Determination of the CO_2 response curve is time consuming and requires patient cooperation. It has not been determined whether an altered CO_2 response curve is a reliable predictor of transient apnea or hypoventilation; therefore, it is not proper to conclude that a normal curve in an awake patient implies normal respiratory control during rest or sleep.[39] Similar criticisms apply to the measurement of mouth occlusion pressure and the response to added mechanical loads. The response to hypoxia has also been measured, but it too requires some degree of patient cooperation. In addition, ethical constraints restrict the use of this technique in the clinical setting, especially in postoperative patients.[73, 76]

RESPIRATORY MONITORING IN THE POSTOPERATIVE PATIENT

In the postoperative setting with spontaneously breathing patients respiratory depression has been assessed either by: (1) CO_2-ventilation response measurements using rebreathing techniques,[81] or (2) noninvasive monitoring of respiration, hemoglobin saturation, and/or arterial blood gases. The measurement of CO_2-ventilation response has provided important and useful information with regard to respiratory depression produced by opioids. Although an altered CO_2 response may indicate depression of central respiratory control, this may have very little practical use in defining clinically significant respiratory depression in postoperative patients. For example, epidural fentanyl is administered by pulse injection or infusion to provide analgesia in postoperative patients with virtually no reports of severe postoperative respiratory complications,[38] and yet the CO_2 response has been shown to be depressed when fentanyl is given by the epidural route.[70, 84] On the other hand, a noninvasive continuous monitoring system fulfills several specific requirements for monitoring respiratory depression in postoperative patients[22]:

1. Continuous measurement is necessary as hazardous incidents such as apnea (central and obstructive), hypopnea, slow respiratory rate, and hypoxemia are missed by the use of discrete measurements.
2. To provide an accurate picture of postoperative respiratory pattern and any changes that occur, the patient should be disturbed as little as possible. Thus, the recording transducers should be noninvasive, comfortable, and unobstrusive.
3. Measurements should not depend on patient cooperation, as postoperative patients at various times may be unconscious, confused, or in pain.[22] Thus, sensitive challenge tests are not as useful in the postoperative patient. In particular, challenge tests may be potentially hazardous in older patients undergoing major surgery and who may be at greatest risk of opioid-induced respiratory depression.

A suitable system for continuous noninvasive monitoring of postoperative patients to detect abnormal respiratory patterns and hypoxemic episodes includes RIP, pulse oximetry, and an indwelling arterial catheter. Sequential and frequent arterial blood gas (ABG) sampling via an indwelling radial arterial catheter provides the most reliable measurement of alterations in Pa_{O_2}, Pa_{CO_2}, and pH. Sampling remote from the patient via extension tubing ensures the patient will not be disturbed. Indwelling arterial cannulae involve minimal risks[96] and are especially useful in patients undergoing major surgery, who constitute an important group for the study of newer analgesic techniques and opioid-induced respiratory depression.[88, 94, 108]

Because of the interaction of sleep and respiration,[78] especially in older patients with systemic disease,[110] Catley[22] has recommended continuous assessment of sleep stage using electroencephalography (EEG), electrooculography (EOG), and electromyography (EMG). This is important in postoperative patients who spend much of their time sleeping if good pain relief is achieved. However, standard sleep stage patterns may be altered by opioids. In addition the administration of opioids is synergistic with sleep in depressing the CO_2 ventilation response.[39]

CLINICAL TRIAL DESIGN FOR THE ASSESSMENT OF ANALGESIC POTENCY AND RESPIRATORY DEPRESSION IN POSTOPERATIVE PATIENTS

Much of the difficulty in assessing the innumerable studies on postoperative analgesia using many different opioids is the lack of uniform study design. The following outline may help in designing comparative clinical trials between opioids to assess analgesic potency and relative respiratory depression in postoperative patients:

1. The patient population should be confined to the same surgical procedure due to very differing analgesic requirements after different surgical procedures (for example, thoracotomy versus laparoscopy).
2. Studies comparing analgesic potency of different opioids should be randomized and double-blinded because of the variability in pain tolerance

and the well-known placebo effect associated with pain relief. Double blinding may be difficult to achieve especially when different routes of administration are compared. The use of an independent observer uninvolved with the treatment regimen may improve the blinding.

3. Where possible subjects should be free of sedative or opioid drugs preoperatively and intraoperatively so that opioid-related effects occurring postoperatively can be related to the study drugs.

4. Because of the effects of sleep on respiration and ABGs,[108, 110] patients should be monitored preoperatively while free of medications using noninvasive techniques (RIP, pulse oximetry, EEG, EOG, EMG) plus an indwelling arterial cannula for ABG sampling if at all possible. Preoperative monitoring will provide within-patient comparison to any postoperative respiratory depression that may be related to opioid administration.

5. Postoperatively, continuous noninvasive monitoring of respiration should be instituted upon arrival in the recovery room and continued for at least 24 hours. Measurements (pain score, ABGs, FEV1, and so forth) should be made immediately before opioid administration (if given by pulse injection) and then at frequent intervals afterwards. In this way time to onset and duration of opioid effect (analgesia, respiratory depression, etc) can be clearly documented. Thus, measurements are performed in relation to drug administration and not at preselected intervals. If opioids are administered by infusion then measurements should be made at frequent regular intervals especially when the infusion rate is changed. If the goal of the investigation is to assess the effect of different opioids on ventilation then respiratory measurements should be performed when subjects have achieved comparable analgesia.

6. Postoperative monitoring should be continued for 24 hours (or longer if possible) with a trained observer present to ensure that artefactual data is not recorded and misinterpreted (for example, movement artefact with pulse oximetry and RIP).

7. Side effects (nausea, vomiting, urinary retention, itching) and serum opioid levels should be recorded, the latter being sampled in relation to drug administration. Serum opioid levels provide a measure of the pharmakokinetics and pharmacodynamics of the opioid gaining access to the vascular compartment. Cerebrospinal fluid levels of the opioid are of importance as well but the measurement is difficult to justify for most clinical trials.

REVIEW OF CLINICAL STUDIES

Routes of Administration

Patient-Controlled Analgesia. No studies have investigated the Co_2 response or used continuous noninvasive monitoring in postoperative patients in whom patient-controlled analgesia (PCA) was used for analgesia. Two reports have documented decreased respiratory rates with PCA administered buprenorphine[41] or increased $Paco_2$ with PCA morphine, meperidine, or ketobemidone.[101] In a study involving patients undergoing upper abdominal operations, more PCA-treated patients had elevated capillary Co_2 levels (45.0 to 54.7 mm Hg) than patients receiving IM or epidural narcotics.[85]

Intravenous Administration. Most studies that have documented the respiratory depressant effects of opioids after either pulse (non-PCA) or continuous intravenous infusion in the postoperative period have used intermittent measurement of respiratory rate, ABGs, or challenge tests (usually Co_2 response). Most of these studies have administered the opioid at the beginning of the surgical procedure and continued postoperatively. Becker et al[10] demonstrated respiratory depression using Co_2 response measurements after fentanyl was used to supplement nitrous oxide anesthesia. A biphasic recovery pattern of respiratory depression was seen in the postoperative period. Similar prolonged depression of ventilation using Co_2 response in the postoperative period when fentanyl is given by pulse injection intraoperatively has been demonstrated by others.[97, 104] In addition, Adams and Pybus[2] have reported severe respiratory depression in three patients 2 to 4 hours postoperatively after moderate to low doses of fentanyl intraoperatively.

Although these studies illustrate opioid-induced respiratory depression postoperatively, they were not designed to measure postoperative ventilatory depression as a complication of postoperative analgesia. In particular, the measurement of pain is conspicuously absent in all of these studies and thus dose-response in terms of analgesia is unknown. Further criticism can be made of studies that have measured the respiratory depressant effects of continuous fentanyl or alfentanyl infusions,[6, 19, 74] all of which used the opioid throughout the surgical procedure to provide analgesia. Two of these studies measured postoperative pain and demonstrated depressed Co_2 response but continued the fentanyl or alfentanyl infusions for only 1 to 2 hours postoperatively.[6, 74] Other case reports have documented life-threatening respiratory depression in the postoperative period after intraoperative alfentanil infusion.[54, 91]

Continuous noninvasive respiratory monitoring of postoperative patients was first used in 1980 by Catling et al.[23] In this study patients undergoing cholecystectomy were randomly given either IM papaveretum or a continuous infusion of papaveretum in the postoperative period and monitored with RIP for 24 hours. Visual analogue pain scores (VAS) were measured daily for 3 days and ABGs were measured 1.5 and 2.5 hours after analgesia was achieved. The IV group had significantly less pain at 24 and 48 hours than the IM group. Although this study would have benefited from blinding techniques and more frequent VAS and ABG measurements, it clearly demonstrated that the IV infusion group (four of seven subjects) developed apneic episodes (AP) and slow respiratory rates (SRR) whereas the IM group was virtually free of these abnormal respiratory patterns (one of seven subjects). The IV group also demonstrated significantly greater $Paco_2$ and decreased Pao_2 after analgesia than the IM group. Whether the IM group would have developed similar abnormalities of respiratory pattern if further papaveretum had been given to improve the VAS is unknown. In a more intensive study Catley et al[21] have used similar noninvasive continuous monitoring to compare two different postoperative analgesic regimens in matched groups of patients undergoing either cholecystectomy or total hip replacement. One group received a continuous IV infusion of morphine whereas the other group received regional anesthesia (intercostal nerve block for cholecystectomy patients and continuous epidural anesthesia for total hip replacement). Although all patients received premedication (papaveretum and atropine) no opioids were given intraoperatively. Patients allocated to the IV morphine infusion were given a pulse injection of morphine at skin closure (0.04 mg per kg). Postoperatively continuous measurement of RIP, oxygen saturation (ear oximetry), EEG, EOG, and EKG were made for at least 16 hours. Pain scores (VAS, verbal rating) were measured at 3 to 4 hour intervals. There were no differences in pain scores between the two groups although no patient reported complete pain relief. Against this background of adequate but not total pain relief Catley et al[21] discovered that 10 of 16 patients receiving the morphine infusion demonstrated a total of 456 episodes of pronounced desaturation ($Sa_{O_2} < 80$ per cent) while breathing room air, whereas no patient in the regional anesthesia group had an episode of pronounced desaturation. In addition, RIP monitoring demonstrated that ventilatory disturbances (central apnea, obstructive apnea, paradoxic breathing, slow respiratory rate, small tidal volume) were all more common in the patients receiving the morphine infusion. The incidence of respiratory disturbances increased with age especially in patients 66 to 75 years of age. Pronounced oxygen desaturation and obstructive apneas only occurred when patients were asleep, and most episodes of oxygen desaturation were associated with obstructive apnea or paradoxic breathing. Central apnea and slow respiratory rate were rarely associated with pronounced oxygen desaturation. Two patients receiving morphine analgesia and who developed numerous apneas and desaturations postoperatively were restudied on the 13th postoperative night while taking no opioid analgesics. No desaturations and very few apneas were seen. Jones et al[47] have shown in a similar study that administration of supplemental oxygen abolishes the pronounced episodes of desaturation, without affecting the incidence of respiratory abnormalities. Measurements of C_{O_2} (EtC_{O_2}, Pa_{CO_2}) were not made in either of these studies.[21, 47]

Spinal Administration. The use of spinal opioids has become widely prevalent in recent years owing to the often perceived superior analgesia that occurs with their use. The problem of respiratory depression and spinal opioids has been reviewed in depth recently.[38] In the following section only prospective clinical studies in postoperative patients will be examined.

Morphine

Intrathecal. There are numerous case reports of severe respiratory depression after intrathecal morphine.[38] However, only one study has assessed chemosensitivity following intrathecal morphine in postoperative patients.[111] Postcesarean section patients were given either epidural morphine (5 mg) or subarachnoid morphine (0.1 to 0.25 mg) or subcutaneous morphine (8 mg). Surprisingly, the C_{O_2} response measured frequently over 24 hours was not significantly altered in the intrathecal group in contrast to the epidural group for whom the CO_2 response curve was significantly depressed for the entire duration of the study.

No studies have used continuous monitoring techniques following intrathecal morphine for postoperative pain. However, several prospective studies measuring intermittent respiratory rate, ABGs, or $EtCO_2$ have been performed. Samii et al,[87] Gjessing and Tomlin,[42] and Moore et al[69] have administered either hyperbaric or isobaric intrathecal morphine for postoperative analgesia. Doses varied from 0.02 or 0.2 mg per kg[87] to 2.5 mg.[69] Varying degrees of significant respiratory depression were found in each study, and it is currently accepted that these doses are larger than required for postoperative analgesia.

Epidural. Several studies have directly assessed CO_2 response after epidural morphine in postoperative patients. There is general agreement that epidural morphine causes early respiratory depression (1 to 6 hours post-dose) comparable to or greater than a similar parenteral dose.[34, 64, 80] This is manifested as an increase in $EtCO_2$, a decrease in the slope of the CO_2 response curve, a decrease in the airway occlusion pressure response, or a decrease in minute ventilation in response to a $PaCO_2$ of 55 mm Hg. Several smaller studies primarily assessing the effectiveness of epidural morphine for postoperative analgesia and in which indirect methods (somnolence, respiratory rate, ABG) detected respiratory depression are summarized in Table 2 and will not be discussed further.

There are few studies that consider the effects of epidural morphine on ventilatory control during the later phase of analgesia. Rawal and Wattwil[80] studied the effects on ventilatory control of 4 mg of epidural morphine given to ten postoperative cholecystectomy patients. Significant respiratory depression was found at 5 and 10 hours postinjection but did not persist beyond this time. In particular, Rawal and Wattwil[80] found that postoperative cholecystectomy patients given epidural morphine had respiratory rates greater than control despite the presence of significant respiratory depression. These studies demonstrate the inadequacy of monitoring respiratory rate as the

Table 2. *Respiratory Depression Detected in Prospective Studies of Epidural Morphine*

REFERENCE	INCIDENCE (PATIENTS)	DOSE
Chambers et al[25]	1/10	10 mg
Crawford et al[33]	2/33	5 and 10 mg
Torda and Pybus[102]	1/130	4 mg
Modig and Paalzow[68]	1/42	5 mg
Weddell et al[106]	1/34	8.4 mg
Klinck and Lindop[51]	1/10	8 mg
Martin et al[63]	1/12	8 mg
Ready et al[82]	2/66	4–5 mg

sole indicator of respiratory depression. Scheinin and Rosenberg[89] compared epidural morphine 2 or 4 mg to either epidural bupivicaine or parenteral narcotics following upper abdominal surgery. In this unblinded study, no clinically apparent respiratory depression was detected, but the $PaCo_2$ measured at 4 hours following anesthesia was found to be significantly elevated in 1 to 3 of 10 patients in each group. Neither respiratory rate nor blood gases were monitored beyond 4 hours. Asantila et al[7] compared thoracic epidural morphine, 4 to 6 mg, with intercostal block or epidural bupivicaine in 51 patients undergoing thoracotomy. Fentanyl was given throughout the anesthetic at a rate of 100 μg per hour and oxycodone was given postoperatively on an as needed basis. Blood gases and respiratory rate were measured at 1, 3, and 24 hours postoperatively, and $PaCo_2$ tended to be elevated in all groups for the first 24 hours postoperatively. However, differences between groups were minor.

In contrast, El Baz et al[37] found severe respiratory depression (defined as loss of consciousness and a $PaCo_2$ of greater than 60 mm Hg) in 8 of 30 post-thoracotomy patients given 5 mg doses of thoracic epidural morphine. Repeat doses were given as required (mean = 4 doses per 24 hours). No other narcotics were administered. One of these eight patients suffered acute respiratory failure after a single dose. Allen et al[5] studied 70 patients given either 0, 2, 5, or 10 mg of epidural morphine for postoperative analgesia. These investigators found no differences in respiratory rate, but with a single blood gas done at 10 hours postoperatively did find a high $PaCo_2$ in the patients given 10 mg. Four of 17 patients in this latter group had an elevated $PaCo_2$ (50 to 54 mm Hg). Parenteral narcotics were given on an as needed basis during the study period. Lanz et al[56] gave 0, 1, 2, 3, 4, or 5 mg of epidural morphine for postoperative analgesia and monitored respiratory rate hourly for 24 hours and in 27 of 139 patients measured blood gases at frequent intervals for the first 12 hours postoperatively. Pentazocine was given on an as needed basis postoperatively. No differences in respiratory rate were detected, but the $PaCo_2$ was elevated by approximately 5 mm Hg in the 5 mg group compared with the controls from 2.5 to 12 hours postoperatively.

The studies cited illustrate some of the problems that make any conclusions concerning the true incidence of significant respiratory depression after spinal opioids difficult. Patients are generally monitored intermittently rather than continuously. Pain scores may vary between groups given the same or different opioids by different routes.[23] In addition, the concomitant use of opioids administered by IM or IV routes when spinal opioids are being studied adds a major confounding variable to the etiology of the respiratory depression.

Two recent studies have specifically addressed the problem of respiratory depression with epidural morphine using indirect monitoring methods. Madsen et al[61] measured respiratory rate and $PaCo_2$ hourly for 10 hours in 18 patients undergoing upper abdominal surgery who were given 8 mg of epidural morphine either intraoperatively or postoperatively. Meperidine, 0.3 to 0.5 mg per kg, was given at the time of extubation to the postoperative group, but no other parenteral narcotics were given. If analgesia was inadequate, epidural morphine, 4 mg, was given on demand at intervals greater than 30 minutes between doses. There were no significant differences between groups, but in both groups the $PaCO_2$ was maximally elevated at 5 to 6 hours postoperatively. Two of 18 patients had respiratory rates of 8 per minute at the tenth postoperative hour, but neither required treatment.

Sandler et al[88] studied respiratory depression in 13 postthoracotomy patients receiving either repeated doses of epidural or IV morphine for postoperative analgesia. In this randomized, double-blind clinical trial, patients were monitored continuously by a trained observer and RIP for 24 hours after surgery. Patients also had ABGs drawn from an indwelling arterial catheter at 2, 6, 12, and 24 hours. Pain scores performed at the same intervals were similar in both groups. These investigators found that the $PaCO_2$ in the epidural group was elevated 2 to 12 hours postoperatively, whereas it was elevated only at 2 hours in the IV group. The respiratory rates were consistently lower in the epidural group. The most interesting results pertain to the use of continuous respiratory monitoring. In the IV group, only one of five patients had an episode of slow respiratory rate (<10 per minute), and none had apneic episodes (15 seconds or longer). In the epidural group, however, five of eight patients had repeated episodes of slow respiratory rate and six of eight had numerous apneic episodes. All patients who demonstrated apnea or hypoventilation had received at least 10 mg of epidural morphine per 24 hours. Pulse oximetry was not used in this study and patients received supplemental oxygen throughout. Whether transient episodes of hypoxemia occurred is unknown.

The use of epidural morphine to provide analgesia following cesarean section deserves particular mention. Depressed CO_2 responsiveness may be present for up to 24 hours following the administration of 5 mg of epidural morphine to postcesarean section patients.[1] However, the incidence of clinically significant respiratory depression appears very low. Kotelko et al[52] gave a single dose of 5 mg of epidural morphine to 276 patients having cesarean section under lumbar epidural anaesthetic. No patient developed a slow respiratory rate (<10 per minute), but one patient was given naloxone for somnolence. Leicht et al[57] prospectively studied 1000 patients given epidural morphine 5 mg following cesarean section. Respiratory depression was defined as a respiratory rate less than 10 per minute and was diagnosed clinically in 4 of the 1000 patients. Two of these patients were observed and required no further treatment. One of the two patients who subsequently received naloxone had a respiratory rate of 9 per minute but had normal blood gases. The one remaining patient had a respiratory rate of 4 to 6 per minute and a $PaCO_2$ of 76 mm Hg and required naloxone. McMorland and Douglas[66] claim in their experience that only 2 of 3000 postcesarean section patients have developed a slow respiratory rate following epidural morphine, and in neither of these patients was there any suggestion of hypoxia of hypoventilation. In each case cited previously respiratory rate or somnolence was monitroed intermittently, and periods of apnea, hypoventilation, or desaturation may have occurred.

Fentanyl

There is one case report of life-threatening respiratory depression following 100 μg of epidural fentanyl.[107] Ancillary sedation perioperatively may have also played a part in the respiratory depression in this instance. In addition, several studies have demonstrated a depression of the Co_2 response curve after epidural fentanyl. Renaud et al[84] examined the respiratory effects of epidural fentanyl given as a 1 μg per kg loading dose followed by a 1 μg per kg per hour infusion in eight postoperative orthopedic patients. Analgesia was described as adequate in seven of the eight patients. No clinically significant respiratory depression occurred. However, the Co_2 response was significantly depressed throughout the 18-hour study period. In a similar study, Ahuja and Strunin[3] gave epidural fentanyl, 1.5 μg per kg, followed 1 hour later by an infusion of fentanyl, 0.5 μg per kg per hour. $EtCo_2$, which was measured continuously, increased slightly within 15 minutes of drug administration, and remained elevated for 1 hour before gradually returning to normal. Although the average increase in $EtCo_2$ was small and not significant, in 2 of 21 patients it rose to approximately 60 mm Hg within 30 minutes, and remained significantly elevated for 90 minutes. Over the 18 hours of the study no late increases in $EtCo_2$ were detected. However, caution should be employed in interpreting $EtCo_2$ when used as a sole monitor of respiratory depression. When patients were monitored immediately postoperatively over a 3-hour period $EtCo_2$ had a regression coefficient of only 0.62 when compared with simultaneous $PaCo_2$ (Turner and Sandler, unpublished data) and thus $EtCo_2$ measurements in spontaneously breathing patients may not reflect $PaCo_2$ accurately.

Several clinical reports support the impression that clinically significant respiratory depression is unusual following either a bolus dose or an infusion of epidural fentanyl. MacKersie et al[59] report ventilation improved in patients with blunt chest trauma following epidural fentanyl as a 100 μg loading dose followed by a 50 μg per hour infusion. Epidural fentanyl has also been reported to provide effective postoperative analgesia with no clinically significant respiratory depression following thoracic and abdominal surgery.[58, 67] These clinical studies were neither blinded nor controlled, and respiratory depression is defined only in terms of respiratory rate or a grossly obvious decrease in the level of consciousness.

Meperidine

Several case reports exist of early respiratory depression following epidural meperidine, but there are no well-documented cases of delayed respiratory depression, and there are no studies that measure the changes in the Co_2 response or use continuous noninvasive respiratory monitoring. Scott and McLure[90] reported two postoperative patients who had severe bradypnea approximately 30 minutes following 50 to 100 mg of epidural meperidine. Both these patients received a narcotic premedication 4 hours prior to the administration of epidural meperidine. Cousins et al[31] reported that two of seven postoperative patients who received 100 mg of epidural meperidine required naloxone for sedation approximately 30 minutes following injection, but respiratory depression per se is not discussed. Two controlled trials have not found any clinically significant respiratory depression. Rutter et al[86] monitored respiratory rate and $PaCo_2$ following a single dose of epidural meperidine (50 mg) given to 20 postoperative patients. Respiratory rate decreased from a mean of 20 to a mean of 16 to 18, but the $PaCo_2$ did not change significantly over the 4-hour postoperative monitoring period. These authors note, however, that in a previous pilot study consisting of eight patients given a single dose of 100 mg of epidural meperidine postoperatively, all patients became heavily sedated with a marked decrease in respiratory rate. Two of these eight patients became unrousable. Baraka et al[8] gave epidural meperidine 100 mg with bupivicaine to 26 healthy primiparous women in labor. Respiratory rate, the only respiratory variable measured, decreased slightly in three patients, but no patient had a rate less than 16. Albright[4] administered epidural meperidine 75 mg to postcesarean section patients and monitored respiratory rate with a continuous apnea monitor for 16 hours. One of 12 patients developed a sleeping respiratory rate of 8, five hours following drug administration. However, the respiratory rate when awake was 18, and the same patient had two subsequent doses without ill effects. Thus, a single dose of epidural meperidine does not seem to exhibit delayed respiratory depression. The effects of repeated doses have not been reported.

Sufentanil

Several investigators have employed epidural sufentanil as either a single dose or as repeated boluses for postoperative analgesia. Following urologic surgery in children[13] epidural sufentanil, 0.75 μg per kg, was not associated with any apneic episodes or abnormally slow respiratory rates. However, monitoring was not continuous nor was apnea defined. Although minute ventilation and $EtCo_2$ did not change significantly, the Co_2 response was decreased significantly at 30 and 60 minutes following injection. Madej and Strunin[60] compared epidural sufentanil with fentanyl for postoperative analgesia in patients undergoing cesarean section with epidural anesthesia. $EtCo_2$ was monitored continuously for 9 hours from the beginning of surgery. Patients received either fentanyl, 100 μg, or sufentanil, 10, 20, 30, or 50 μg. Although 4 of 50 patients developed bradypnea of 8 per minute within 20 minutes of opiate administration (three received fentanyl and one received sufentanil, 50 μg), none of these four had a clinically significant elevation of $EtCo_2$. No episodes of apnea were detected. However, the validity of $EtCo_2$ monitoring as a sole measurement of respiratory depression awaits validation (vide supra). Whiting et al[108] administered sufentanil, 30, 50, or 75 μg, via a lumbar epidural catheter to post-thoracotomy patients. Repeat doses were given as required, but at intervals of not less than 30 minutes. Patients were monitored continuously using RIP for 24 hours postoperatively and arterial blood gases were measured at 30 and 60 minutes and then at four hourly intervals. In all groups the $PaCo_2$ was significantly elevated at 30 minutes and apneic episodes occurred in over 50 per cent of patients. In the group receiving 75 μg, three of seven patients developed severe respiratory depression. One of these three had a respiratory arrest requiring intubation after a single dose. Van der Auwera et al[103] compared single doses of either epidural sufentanil (50 μg) with epidural morphine (5 mg) in patients undergoing abdominal surgery. Respiratory rate and $PaCo_2$ were monitored intermittently for 12 hours. No significant increase in $PaCo_2$ was seen but 2 of 15 patients given sufentanil developed marked bradypnea within 10 minutes of the dose. Several case reports also document the occurrence of severe respiratory depression following either single or repeated doses of epidural sufentanil. Blackburn[14] reports two patients who suffered respiratory arrest following four to seven doses of epidural sufentanil, 50 μg, over 20 to 22 hours. Vercauteren et al[105] report extreme bradypnea and hypercapnea in two post-thoracotomy patients following a first dose of 50 μg given postoperatively. These patients received IV morphine 0.3 mg per kg intraoperatively.

Other Opioids

Numerous other opioids have been administered via the epidural route for postoperative analgesia. Diacetylmorphine has been reported to cause both early and delayed respiratory depression when administered by both the epidural and intrathecal routes.[9, 29, 30, 46, 62] The incidence of clinically significant problems is unknown. In volunteers, epidural alfentanil, 15 μg per kg, did not alter resting $PaCo_2$ but did decrease the Co_2 response for at least 90 minutes following administration. The same dose of alfentanil, given intramuscularly, depressed the Co_2 response curve at 15 but not 45 or 90 minutes.[77] Limited clinical evidence suggests that 30 μg per kg, but not 15 μg per kg, may produce early, severe respiratory depression.[26] Epidural buprenorphine, a lipophilic, mu receptor partial agonist is associated with early and persistent respiratory depression in both patients[43] and volunteers.[79] Buprenorphine dissociates very slowly from mu receptors; as a result, naloxone, even in large doses, may be ineffective in reversing respiratory depression once it develops.[27] Abboud et al[1] measured the Co_2 response in postcesarean section patients who received either epidural morphine or butorphanol. Co_2 responsiveness was depressed for at least 12 to 16 hours following 2 to 4 mg of butorphanol. Morphine had a greater depressant effect, but also provided more complete analgesia.

SUMMARY

Numerous studies have been performed in postoperative patients to assess respiratory depression when opioids are used for analgesia. The largest number of studies relate to the use of epidural opioids postoperatively. In general, respiratory depression can be demonstrated when opioids are used if highly sensitive challenge tests are used (Co_2 response). However, continuous noninvasive monitoring techniques are more suitable to demonstrate clinically significant respiratory depression. Further studies using these techniques are required to assess whether different opioids or routes of administration confer advantages in terms of improved analgesia with less respiratory depression.

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Pain Management Following Trauma and Burns

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Accidental injury remains the leading cause of death in the United States up to age 44, and is responsible for more productive years lost than any other single disease process.[29] Trauma patients are generally young, otherwise healthy, and frequently have multisystem injuries. Because of the typical seriousness and acuity of post-traumatic injuries, and the therapeutic "tempo" with which they must be managed, treatment of injury-related pain is generally accorded a lower management priority and is not infrequently overlooked.

The initial therapeutic goals in the management of the injured patient include (1) preservation of life, (2) preservation of limb, (3) preservation of function, (4) avoidance of complications, and (5) avoidance of diagnostic delay. Although the treatment of discomfort and anxiety is a desirable goal in the management of these patients, the pharmacologic interventions used to accomplish these goals often fall at cross purposes, particularly in the early hospital course, with the therapeutic goals of the trauma surgeon.

The undesirable side effects of most analgesics and many sedative hypnotics potentially interfere with the management of the acute trauma patient. These include the following: respiratory depression; depression of cough reflex; depression of level of consciousness; hypotension; potential masking of injuries by blunting the pain response to physical examination; depression in gastrointestinal motility, and urinary retention.

Therapeutic goals of the pain management following trauma and burns, in addition to the relief of pain and the alleviation of anxiety, include the following: (1) restoration of ventilatory function in patients with blunt chest trauma; (2) amelioration of the effects of various nox-

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ious stimuli on intracerebral pressure in patients with severe closed head injuries; (3) initial control of systemic hypertension in patients with head injuries; (4) improvement in the efficacy of mechanical ventilation in patients with severe derangements in gas exchange; (5) facilitation of the re-establishment of normal diurnal sleep patterns, particularly in intensive care unit patients; and (6) facilitation of burn wound care and dressing changes in the intensive care or ward setting.

The process of balancing the primary therapeutic goals of injury management, with the goals of pain management while avoiding or minimizing analgesic and sedative-related side effects, is a complex task and one that requires a cooperative team effort on the part of the pain or critical care service and the primary surgical service. Once management priorities have been established in a given patient, the timing, method, and frequency of pain-related intervention should be determined.

As with any therapeutic intervention, the effects of pain control must be closely monitored, both for efficacy, and for complications and side effects. Monitoring the effect of analgesics is usually imprecise and very subjective. Perception of pain varies widely among medical staff and evidence suggests that pain is frequently undertreated.[44] Therapeutic goals other than relief of subjective pain may be more easily monitored. For example, the restoration of ventilatory function in blunt trauma patients may be monitored by the use of bedside pulmonary function tests. The effect of sedation and analgesia on a ventilated patient, whose discomfort is causing agitation and who is "fighting" the ventilator, may be monitored by improvement in peak inspiratory pressure and gas exchange. Most side effects of pain management may be anticipated (for example, paradoxical agitation with ketamine, or pruritis with epidural opiates), and the pain management plan should include the treatment or alleviation of these anticipated side effects.

SPECTRUM AND FREQUENCY OF MAJOR TRAUMATIC INJURY

The conscientious management of pain potentially offers substantial therapeutic benefits in certain types of traumatic injuries. For example, pain-related impairment of ventilatory function seen with blunt chest and abdominal trauma may be improved by alleviation of discomfort and anxiety. Opiate analgesia may be of benefit in the treatment of intracranial pressure (ICP) in severe head injuries. Oxygen consumption and metabolic rate may be reduced by relief of pain and muscular spasm seen with major skeletal injuries such as pelvic fractures, long bones of the lower extremity, or axial spine fractures.

Major injuries posing problems in pain management are common. The frequency of major chest, head, and skeletal injuries admitted to the University of California San Diego Medical Center between 1985 and 1988 are listed in Table 1. One out of two blunt trauma patients

Table 1. *Incidence of Major Injuries and Pulmonary Complications in 3419 Blunt Trauma Patients (University of California, San Diego 1985 to 1988)*

	NO.	%
Severe closed head injuries	404	12
Multiple rib fractures	487	14
Pulmonary contusion	173	5
Abdominal injuries	350	10
Axial spine injuries	490	14
Lower extremity fractures	549	16

will have one or more of these serious injuries. Nineteen per cent will have multiple injuries. One of the frequent problems complicating management of pain is depression of level of consciousness, either secondary to head injury or to ingested alcohol or drugs. In a recent study of blunt trauma patients in San Diego County, 11 per cent of patients admitted to one of five regional trauma centers had depression of level of consciousness consisting of a Glasgow Coma Score of 10 or less.[42] Alcohol or drugs were involved in 50 per cent of these patients.

In addition to the problem of multiple injuries and a depressed level of consciousness, 14 per cent of 4434 blunt and penetrating trauma patients at our institution required mechanical ventilation at some point in their hospital course with the attendent problems of discomfort, anxiety, and weaning from mechanical ventilation. While the majority of patients admitted to a major trauma center have limited or single-system injuries that can be managed using conventional, parenteral, or oral analgesics, a significant percentage will have complex problems and multisystem injuries requiring a carefully planned approach to the relief of pain and anxiety.

CARDIORESPIRATORY RESPONSES TO MAJOR TRAUMA AND BURNS

Severe head injury and hemorrhage remain the most common cause of early death in trauma patients,[3] and derangements in cardiorespiratory function are common in patients immediately following injury. Of 4434 trauma patients admitted to UCSD within a 4-year period, 604 (13.6 per cent) were hypotensive on arrival (blood pressure less than 90). An additional 1341 (30 per cent) had alterations in ventilatory pattern as defined by the respiratory component of the trauma score.[15] These physiologic changes seen soon after injury are relative or absolute contraindications to the use of agents that may exacerbate hypotension or produce respiratory depression. The use of narcotic or sedative agents in these patients is ill advised until both restoration

Table 2. *Causes of Shock and Respiratory Failure Following Trauma*

SHOCK	RESPIRATORY FAILURE
Hypovolemia/hemorrhage	Severe head injury
Tension pneumothorax	Shock
Brainstem herniation	Pulmonary contusion
Myocardial contusion	Aspiration
Cardiac tamponade	Spinal cord injury
Spinal cord injury (sympathectomy)	ARDS (including sepsis)
Blood or drug reaction	Pneumonia
Sepsis	
Air embolus	

of ventilatory function or control of the airway and breathing in addition to volume replacement and control of hemorrhage have been accomplished.

Other analgesic methods that may provoke further deterioration in cardiovascular or pulmonary function should also be avoided. Extensive epidural block, for example, is contraindicated in most trauma and burn patients early in their hospital course because of the potential for the associated sympathectomy effect to exacerbate the hypovolemia that frequently exists in these patients. Cardiac arrest has been reported in this situation.[35] In addition, muscular blockade may both inhibit ambulation and impair function of the ventilatory muscles.

The causes of shock and respiratory failure seen regularly in trauma patients are listed in Table 2. Hemorrhagic shock with attendant diminished blood flow to the diaphragm may in turn produce ventilatory failure. Drugs such as opiate analgesics that produce central hypotension may severely exacerbate the effects of cardiovascular or respiratory compromise. Major burn injury (greater than 25 per cent body surface area in adults) may also produce profound decreases in intravascular volume, similar to hemorrhagic shock, that result in maximal vasoconstriction by the patient to maintain blood pressure. Any agents that are capable of producing hypotension, either by centrally mediated or locally mediated vasodilatation, are contraindicated until intravascular volume is adequately restored. Drugs that act as myocardial depressants must also be avoided.

STRESS RESPONSE

The stress response following injury is mediated both by hormones resulting from stimulation of the peripheral, central, and autonomic nervous systems, and by humoral factors such as kinins, leukotrienes, and prostaglandins arising from tissue injury.[35] The hormonal increases induced by trauma or burns are similar in kind but many fold greater than those from major surgery.[30] Catecholamines, cortisol, and glucagon (the counter-regulatory hormones) all increase in response to injury.[25, 37] Stress hormones induce the endocrine/metabolic state of hyperglycemia, insulin resistance, and increases in gluconeogensis lipolysis, and protein catabolism.[19, 76] Vasopressin, growth hormone, and β-endorphin levels are also elevated. Impaired immune response, principally characterized by a reduction in number and function of lymphocytes and granulocytosis is also an important component of the stress response.[65]

Many factors may be involved in initiating the stress response. Shock, acidosis, hypothermia, anxiety, hypoxemia, in addition to injury pain, occur frequently in trauma and burn patients, and correction of these abnormalities are given top management priority.

The degree to which the institution and maintenance of post-injury analgesia blunts the endocrine/metabolic response to trauma, assuming such a goal is desirable, has not been well defined. Limited data are available from studies on elective surgical patients, however.

Intermittent parenteral opiate analgesics have little influence on hormone level reduction. High-dose narcotics will blunt the hormonal response, but only while maintained at a high level, limiting the usefulness of this method outside the operating room.[7] Epidural opiates, despite providing excellent pain relief, exert only a modest reduction on stress hormone levels, indicating that alleviating pain is only a part of stress-response reduction.[17, 31]

Epidural local anesthetics have been shown to significantly diminish the stress response in a select group of patients, primarily patients undergoing lower abdominal procedures (hysterectomy) or lower extremity surgery (total hip replacement).[36] Besides lower hormone levels, some studies have noted improved nitrogen balance[11] and enhanced immunocompetence.[58] A T4–S5 block appears to be necessary despite the fact that excellent pain relief could be achieved with a T8 level. The more extensive blockade acts to block somatic and sympathetic afferents that may enter the spinal cord as high as T4 from lower abdominal stimuli. As expected, epidural opiates would not affect these nerves, supporting the observation of their minor effect on stress hormone reduction.

The effect of epidural local anesthetics on upper abdominal and thoracic surgery patients is unclear, but the effect is much less when compared with lower abdominal surgery patients.[2, 27] Possible explanations include incompletely blocked vagus nerves or incomplete sympathetic block. The latter hypothesis is strengthened by the observation that celiac plexus block may affect hormone level reduction.[73] Insufficient somatic afferent block is also a possibility.

A major limitation in extending the findings in elective surgery patients to trauma and burn victims is that the elective patients had epidural blockade prior to the stressful event. If a block is initiated following trauma or major surgery, it has been shown to be less effective in stress hormone reduction.[48] In addition, trauma and burn patients may have many factors inducing the stress response that do not exist in elective surgical patients, and the degree of injury and tissue destruction is typically much greater than with elective surgical patients.

The role of β-endorphins in the physiologic response to injury has recently generated a great deal of interest but only limited information is available thus far. β-endorphin levels increase in burn patients and the levels have been shown to correlate with the degree of pain.[68] They also appear to be temporally related to the degree of immunosuppression following traumatic injury,[41] and have been correlated with the risk of sepsis.[40] Early animal studies have further demonstrated that β-endorphins have been associated with myocardial depression and hypotension.[51]

These observations have prompted attempts to employ naloxone to block opiate receptors. The results of this approach have been variable. In certain species, hypotension, shock, and death were lessened with naloxone,[26] whereas others have reported diminished survival in animals with the use of naloxone in traumatic shock.[71]

Whether amelioration of post-burn or post-injury pain will have any therapeutic benefit with respect to modulation of β-endorphin levels remains to be seen, and the potential effects of pain control in reducing post-injury immunoincompetence and protein catabolism remain largely uninvestigated. The relative importance of the neuroendocrine changes compared with the many humoral factors elaborated following burns and trauma is also unclear, and until further data are available, it seems prudent to carefully define therapeutic goals of which the effective relief of pain is both desirable and obtainable.

MISSED INJURIES AND DELAYED DIAGNOSIS

Despite the variety of diagnostic methods available to identify all significant injuries in the trauma patient at the time of admission (computerized tomography, diagnostic peritoneal lavage, radiologic studies), in many instances the initial performance of these studies will depend on findings of a careful initial physical examination. In addition to the initial examination, careful follow-up examinations are vitally important in the early diagnosis of certain types of injuries. A patient with a developing epidural hematoma, for example, may have an initially normal level of consciousness followed by subsequent obtundation. Patients with hemoperitoneum or even bowel perforation, may initially have a benign abdomen, only to subsequently develop signs of peritonitis on follow-up examination.

Both systemic and particularly epidural analgesics, may potentially mask the physical signs of serious underlying injury. If analgesic methods are to be employed that put the patient at risk for a blunted response to developing signs of injury, serious consideration should be given to reliably excluding injuries using available diagnostic methods. For example, diagnostic peritoneal lavage should be considered in all patients with multiple rib fractures who are candidates for epidural catheters in order to reliably exclude the presence of a significant intra-abdominal injury. Protocols that rely on serial physical examination as a means of diagnosing injury may not be compatible with the institution of certain analgesic methods (such as, epidural opiates).

SPECIFIC CLINICAL PROBLEMS IN POST-INJURY PAIN MANAGEMENT

Blunt Chest Injury

Blunt chest injury, including multiple rib fractures, flail chest, pulmonary contusion, with or without hemopneumothorax, occur frequently (Table 1), mostly as a result of vehicular accidents. Multiple rib fractures produce significant chest wall edema that may or may not be associated with underlying local lung edema in an area of pulmonary contusion. This results in decreased chest wall and lung compliance and a greater inspiratory work of breathing. Problems with increased ventilatory work are compounded by the severe pain commonly associated with these types of injuries. Elderly patients who are more at risk for the development of pulmonary complications may not initially appear to be in any distress. When the vicious cycle of pain and increased ventilatory work causing decreased tidal volumes, decreased functional residual capacity, increased shunt, and decreased ability to clear secretions is established, significant impairment in gas exchange, lobar segmental collapse, and pneumonia may ensue. Patients with little or no ventilatory reserve may require intubation and mechanical ventilation as a consequence.

The major therapeutic goals in the pain management of blunt chest trauma include the restoration of pulmonary function and the avoidance of significant respiratory depression. Conventional bolus opiate dosing has the major disadvantage of maintaining the patient at that therapeutically desirable level of good analgesia without respiratory depression only for short periods of time. Previous studies[22] have observed the effect of bolus narcotic on ventilatory function. A number of alternate methods of analgesic administration have been developed over the years in an attempt to avoid some of the side effects of conventional opiate dosing.

The use of postoperative or post-injury intercostal nerve blockade using local anesthetics has been found effective in a number of studies. Bridenbaugh et al[12] found that there was a more pronounced depression in PaO_2 following intermittent narcotic bolusing when compared with intercostal nerve block analgesia. Other reports[54, 70] have shown significant improvement in ventilatory function with intercostal nerve blockade. The disadvantages of this technique include its relatively short duration of action (6 to 12 hours) and the risk of iatrogenic complications, specifically pneumothorax.

The use of epidural administration of opiates and local anesthetics has been associated with significant improvement in ventilatory func-

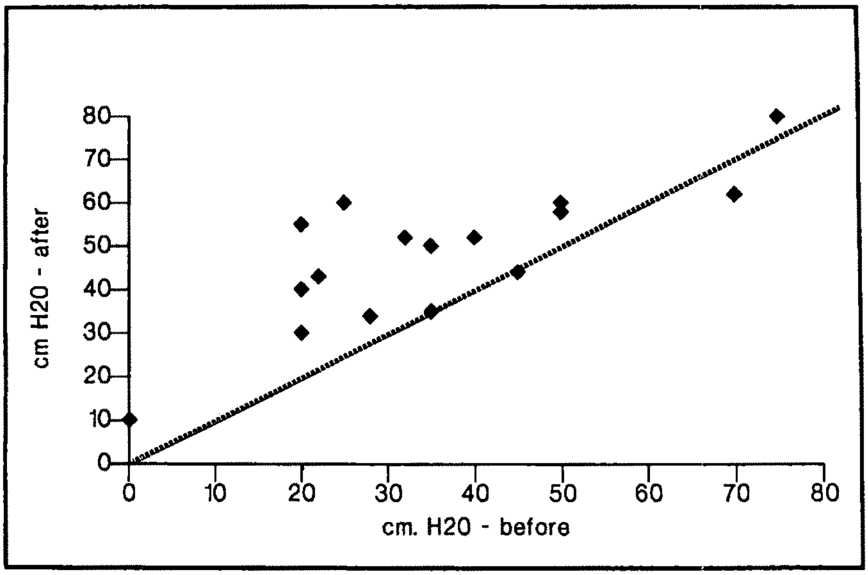

Figure 1. Maximum inspiratory pressure before and after fentanyl epidural analgesia. (*From* Mackersie RC, Shackford SR, Hoyt DB, et al: Continuous epidural fentanyl analgesia: Ventilatory function improvement with routine use in treatment of blunt chest injury. J Trauma 27:1207–1212, 1987; with permission.)

tion. Dittmann and Wolff[21] noted improvement in functional residual capacity, lung compliance, and airway resistance in blunt chest trauma patients receiving bupivicaine epidural analgesia. Rankin and Comber[56] also reported successful management of blunt chest injury using a combination of bupivicaine and morphine. In a review of 40 patients at the University of California San Diego Medical Center,[43] we found significant improvements in both maximum inspiratory pressure and vital capacity after the institution of continuous epidural fentanyl analgesia (Figs. 1 and 2). This method was associated with only one instance of respiratory depression and 95 per cent overall efficacy rate, without the need for additional systemic analgesics. Patients generally required between 50 and 100 μg per hour of epidural fentanyl (5 μg per ml of normal saline).

The use of epidural narcotics as opposed to local anesthetics has the advantage of avoiding some of the side effects of local epidural anesthetics including sympathetic blockade, hypotension, and motor blockade.

Cryoanalgesia, accomplished by freezing the involved intercostal nerves using a cryosurgical probe requires direct access to the nerve such as occurs at the conclusion of a thoracotomy. This technique has limited applicability for trauma patients in whom the vast majority will be treated without operation. Reports regarding restoration of pulmonary function in post-thoracotomy patients using

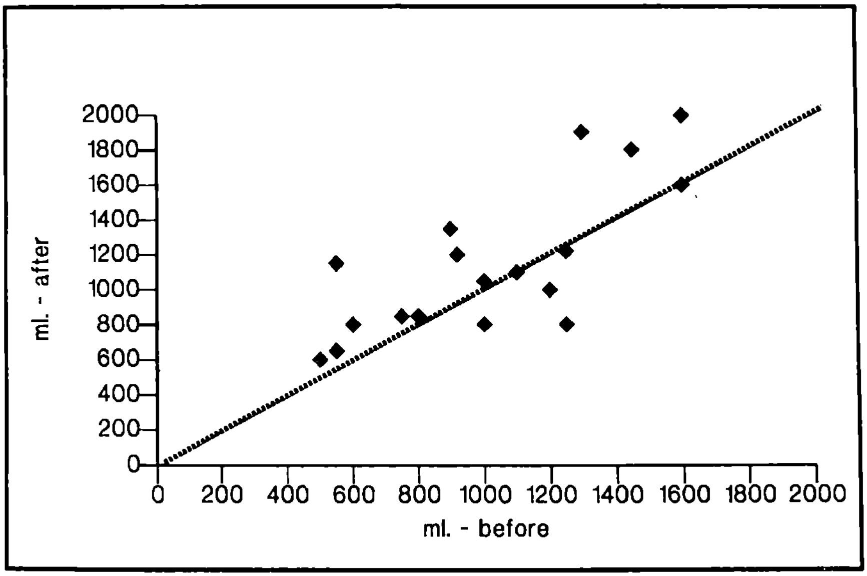

Figure 2. Vital capacity before and after fentanyl epidural analgesia. (*From* Mackersie RC, Shackford SR, Hoyt DB, et al: Continuous epidural fentanyl analgesia: Ventilatory function improvement with routine use in treatment of blunt chest injury. J Trauma 27:1207–1212, 1987; with permission.)

cryoanalgesia have not been promising. Roxburgh et al[61] carried out a prospective randomized trial to evaluate cryoanalgesia, but were unable to demonstrate any significant difference between the trial and control groups. Another study by Katz et al[33] found similar results.

The intermittent instillation of local anesthetics into the pleural space is currently under investigation as a means of treating post-thoracotomy pain and patients with multiple rib fractures. This technique typically involves the infusion or instillation of a 0.5 per cent bupivicaine solution into the pleural space via a catheter specifically inserted for the purpose. Although these studies suggest that intrapleural anesthesia may be effective in patients with thoracotomies[32] and rib fractures,[59] there are no data on restoration of pulmonary function, and little or no experience in patients with hemopneumothorax.

The use of transcutaneous electrical nerve stimulation (TENS) to provide postoperative analgesia has received a fair amount of attention in recent years. There is little experience with the use of TENS in patients with blunt chest trauma. The efficacy of TENS in post-thoracotomy patients is equivocal. Warfield et al[75] showed improvement in pain score of post-thoracotomy patients using TENS, but no change in opiate requirement. In another study[60] only 22 per cent of thoracotomy patients treated with TENS did not require additional opiates postoperatively. The observations regarding the restoration of ventilatory function with the use of TENS have also been variable. Stratton and Smith[66] showed improved forced vital capacity following TENS therapy, whereas in another study, post-cholecystectomy patients failed to show any change in peak expiratory flow rates with the use of TENS.

Patient-controlled analgesia (PCA) is another method of analgesic administration that offers the advantage of high patient acceptance, excellent control of pain, and avoidance of excessive sedation. Its effect on restoring ventilatory function and practicality for usage in patients with multisystem injury, however, has yet to be demonstrated.

Neurologic Injury

Trauma patients who present with an altered level of consciousness present a unique challenge in regard to pain management. Patients are frequently combative and sometimes described as "screaming in pain." Major head injuries are common and must be assumed present until proven otherwise. The frequent association of alcohol and drugs may further confuse the clinical picture, and other causes including underlying psychiatric illness, shock, and hypoxia must be considered.

While the administration of opiate analgesics is generally contraindicated in patients who are hypovolemic or who are at risk for any degree of respiratory depression, they may have salutary effects on intracranial pressure in head trauma patients once control of ventilation has been established. Pain, via its effect on CNS excitation and increases in blood pressure, cardiac output, and cerebral blood flow, is deleterious to the injured brain. Studies have documented the ability of even low-dose morphine to reduce oxygen consumption in some areas of the brain,[13] and there may also be some benefit in reducing cerebral blood flow by blunting the effects of noxious stimuli (pain).[72] Opiate administration cannot be based on subjective responses in head-injured patients,[46] so autonomic responses (heart rate, blood pressure, respiratory changes) to various stimuli must be relied on as clinical indices of analgesic response. The relative merit of different opiates in head-injured patients has not been studied, but historically, morphine has had the most widespread usage. The use of local anesthetics or opiates administered via the epidural route has not been studied in head-injured patients. The epidural route of administration offers advantages over parenteral opiates in patients with multiple or extensive trauma (for example, flail chest) in whom frequent neurologic evaluations are necessary (for example, mild closed head injury). Equipotent analgesia is associated with less CNS depression and further, any obtundation may be reversed with naloxone, usually without significant loss of analgesia.

Analgesia and Sedation in the Intensive Care Unit

The ideal agent for sedation and analgesia in critically ill patients does not exist. Characteristics of the ideal drug would include simplicity of administration, lack of blood or tissue accumulation, short half-life, possibly a reduction of stress response, and no adverse effects on any major organ system. Benzodiazepines and opiates are the principal sedative/analgesic drugs used in the intensive care until (ICU).[47] They are far from ideal. Diazepam, the most frequently used sedative, suffers from the accumulation of active metabolites that may delay return to consciousness and make neurologic assessment difficult. Midazolam by infusion and intermittent lorazepam lack active metabolites and offer some advantages over diazepam, although prolonged sedation is observed under certain circumstances. The development of a benzodiazepine antagonist will, it is hoped, alleviate this problem. A marked variability has been noted with midazolam infusions, with a serum half-life of over 10 hours not an infrequent occurrence.[52]

Opiates are extensively employed in the ICU, with morphine having the greatest popularity. The half-life of morphine is relatively long, however, and significant cardiovascular changes (for example, vasodilation) may occur. Histamine release is an occasional problem. Accumulation may occur primarily in patients with impaired renal function, and this may result in the morphine level remaining elevated enough to impair consciousness and ventilatory drive for days after it is stopped.[4] Fentanyl has certain advantages over morphine (for example, better cardiovascular stability) but with prolonged administration, accumulation and tolerance may occur. Alfentanil has the advantage of a short half-life and may hold promise when used as an infusion. All narcotics depress gastrointestinal motility, already a problem in trauma and burn patients.

Epidural opiates have the advantage of avoiding, to a significant degree, the cardiovascular and respiratory effects of systemic opiates. They may have the additional advantage of decreasing patient-ventilator dyscoordination sometimes observed in agitated ICU patients.[57] Epidural hematomas and epidural abscess as the result of catheter placement may present potentially higher risks as a result of coagulopathies and immunosuppression that critically ill patients are more prone to develop.

The practice of using muscle relaxants as substitutes for analgesia or sedation to prevent a patient from "fighting" the ventilator is to be deplored. Numerous accounts exist of ICU patients recalling the extremely disturbing experience of being paralyzed and insufficiently sedated.[53] Occasionally, patients with severe derangement in gas exchange (for example, adult respiratory distress syndrome) may require paralysis to minimize airway pressures, improve gas exchange, and reduce the chance of barotrauma or hemodynamic compromise. Paralysis may also be used as an adjunct in treating intracranial hypertension following head injury. In all cases, however, appropriate analgesia and sedation must be provided if muscle relaxants are to be used. Paralytic agents should be held on a regular basis in order to assess the adequacy of analgesia/sedation, particularly in patients without depressed level of consciousness.

Agitation and asynchronous ventilatory patterns in patients on mechanical ventilation should be viewed as a possible clue to a problem and not result in the reflex administration of "quieting" agents. Hypoxemia, airway obstruction, hypoventilation, and acute abdominal pain may all initially present as agitation and may prompt inappropriate treatment with analgesics, sedatives, or paralytic agents.

In conclusion, there is no ideal ICU sedative or analgesic. Opiates and benzodiazepines are used most extensively. Epidural narcotics and shorter-acting sedatives offer considerable promise. The role of PCA in the ICU has not been explored. The sedative-analgesic choice should be individualized, taking into account numerous factors such as analgesic requirement, previous drug history, cardiovascular status, hepatic and renal function, and neurologic condition of the patient.

Extremity and Spinal Trauma

Injuries to the axial spine and extremities are among the most frequent in blunt trauma patients (Table 1). Because these injuries are frequently associated with major thoracoabdominal injuries, the method of pain management may be more appropriately directed toward those injuries. Muscular spasm is a major component of fractures, both of the axial spine and of the extremities. In fractures involving the lower extremity, spasm can be minimized early in the post-injury course by application of appropriate traction or splints. Early post-injury stabilization of the fractures reduces blood loss, alleviates pain, and may have salutary effect on pulmonary and infectious complications.[62] Early fixation of fractures should be a high priority in patients with major skeletal injuries. Pain produced by muscle spasm is also a feature in patients with fractures of the axial spine. Although there is little data available in trauma patients, there is evidence to support the use of a combination of antispasmotic and opiate analgesics in the treatment of spasm.[9] In patients with more severe fractures associated with soft-tissue injuries in the lower extremity, significant relief may be obtained by the use of epidural opiates.

Patients with traumatic amputations represent a special problem in pain management. In the acute phase, amputation pain may be managed using conventional systemic or epidural opiates. Patients undergoing replantation for upper extremity injuries have the problems of pain, decreased circulation secondary to vascular spasm, and a need for complete immobility of the extremity. The use of axillary plexus catheters with continuous infusion of local anesthetics has been found both to improve the circulation by a sympathectomy effect, provide good regional analgesia, and facilitate immobilization by producing muscle relaxation.[8, 50] Catheters may be left in for up to 1 week following replantation with minimal complications.

Phantom limb pain presents a more chronic problem and occurs frequently in patients after limb amputation. Up to 40 per cent of patients with lumbosacral plexus or brachial plexus avulsion may experience severe phantom pain[5] and up to 85 per cent of patients may report some phantom limb discomfort.[63] A number of agents have been evaluated in the treatment of phantom limb pain, but there is little data available in the way of prospective randomized studies from which to draw conclusions. Opiates are probably of little long-term benefit. Beta blockers,[45] anticonvulsants,[23, 67] tricyclic antidepressants, and neuroleptics[64] have all been used with varying degrees of success to improve phantom limb pain following amputation. The placement of spinal dorsal root entry zone (DREZ) lesions is generally reserved for patients who fail to obtain adequate relief from pharmacologic agents. In a study of 21 patients with brachial plexus avulsions, Nashold and Ostdahl reported good relief in 67 per cent with the placement of DREZ lesions.[49]

Spinal cord stimulation and TENS have also been evaluated in the treatment of post-amputation phantom limb pain. Krainick and Thoden[39] reported good results in approximately half of their amputees at 2 years using spinal column stimulation. Although this method improved the "background" pain experienced by these patients, the more severe, acute attacks and pains were not generally alleviated. Other studies have reported TENS response rates of 45 to 65 per cent,[28] and it continues to be an important modality in the treatment of phantom limb pain.

Analgesia for Wound Management

In addition to major burn injuries, post-traumatic soft-tissue injuries involving either extremities or torso often require local wound care consisting of frequent debridement, irrigation, and dressing changes. The performance of these procedures is generally associated with an extreme amount of pain requiring a conscientious and thoughtful approach to pain management. These patients, in addition to their physical discomfort, usually experience a state of anxiety regarding wound treatment, and may also be clinically depressed as a result of their prolonged hospitalization.[16] The question of when analgesia becomes anesthesia, and whether or not it is appropriate to administer a general anesthetic in an ICU setting, must sometimes be addressed in these patients. Answers to these questions will depend on the facilities and staffing available at a given institution. As a rule, however, the staffing and monitoring equipment available in the ICU must be essentially the same as that in the operating room. It has generally been our practice to perform major post-traumatic wound debridement in the operating room owing to a variety of factors, including better facilities, the avoidance of disruption of ICU routine, the relative lack of sterility in ICUs, and the lack of equivalent lighting and equipment.

For patients undergoing debridement or a dressing change in the burn or ICU setting, the alleviation of as much discomfort as possible, and the anxiety associated with the procedure should be primary goals. There is no general agreement as to the optimum way to provide debridement analgesia. A number of methods have been used in the past including opiates, ketamine,[20] nitrous oxide,[6] and inhalational agents.[14] In a survey of American burn units, Perry and Heidrich[55] found that roughly two thirds of burn units rely on morphine or meperidine administered either intramuscularly or intravenously as their drug of choice. Approximately half of these burn units used an additional psychotropic drug (diazepam, hydroxyzine, chlorpromazine, or ketamine) in conjunction with narcotics. There was extreme variability in the dosages used, varying from 35 mg of parenteral morphine to 30 mg of oral codeine for similar types of debridement. Whatever the dose, there is some evidence that suggests that analgesic requirements for burn analgesics may be underestimated. The authors also found that the perception of pain in patients by the staff administering the debridement is extremly subjective and appears to vary more with experience on the job than it did between nurses and physicians.

Opiates used for burn and post-traumatic wound debridement have the advantages of providing excellent analgesia, and being relatively short acting and reversible, particularly agents such as fentanyl. Respiratory depression continues to be a problem except for patients on a mechanical ventilator. Hypotension occurs infrequently and can be treated by the administration of fluids and naloxone. The use of intramuscular ketamine (4 mg per kg) in the excision of burn eschar has been reported by Demling et al.[20] They concluded that the drug was extremely safe and was associated with very few side effects. They found the incidence of hallucinations and excitation, the so-called emergent reactions, present in about 10 per cent of patients. Laryngospasm, which has been reported as a possible complication, was not observed.

Other methods of pain management in burns that have been reported include the application of TENS,[38] use of pain "cocktails," and hypnosis. There is no clear superiority of one method over another, and all appear to have some efficacy. The major stumbling block continues to be a large variation in the perception of debridement pain by the treating medical staff. Clearly a more uniform, objective means of quantifying pain is badly needed.

CONCLUSION

The physiologic response to major injury is complex and involves all of the major organ systems. Cardiovascular, pulmonary, neurologic and hormonal responses are of particular importance in regard to the management of pain in these patients. Analgesic agents and methods that may potentially interfere with the diagnosis and treatment of multiply injured patients should be used carefully during the initial resuscitation. Their use in the later phases of patient management, however, may result in significant improvement in pulmonary, neurologic, and metabolic function. The role for newer pain control techniques such as PCA and TENS has not been defined in the trauma patient.

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Organization of an Acute Pain Service: Training and Manpower

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The optimal care of surgical patients includes effective control of incisional pain.[1, 8] Despite advances in the knowledge of pathophysiology, pharmacology of analgesics, and the development of more effective techniques for postoperative pain control, many patients do not receive adequate analgesia.[1, 2, 4, 5, 8, 12, 14] Attention is beginning to focus on new in-hospital services created to improve the management of acute pain. We have described the development and early experience of an anesthesiology-based postoperative pain management service.[10] The purpose of this article is to provide additional detail regarding the organizational and operational aspects of this service. What we describe is well suited to our institution. Differences in surgical populations, nursing practices, and medical preferences will be found in other institutions. Their unique needs would be expected to result in some modification of the service we have developed.

Anesthesiologists are a logical choice to provide pain relief in the immediate postoperative period because they are familiar with the pharmacology of analgesics, aware of the short- and long-term effects of drugs given intraoperatively, knowledgeable about pain pathways and their interruption, and skilled in techniques available to provide superior pain control.

One of the most important and effective therapeutic modalities to become available to control postoperative pain has been epidural opiate analgesia (EOA).[3] Unfortunately, a number of factors have previously limited its widespread use. These include the time required by anesthesiologists to initiate and supervise treatment, lack of struc-

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tured interdisciplinary programs in hospitals to treat postoperative pain, and fear of life-threatening respiratory depression. Any program planning to offer EOA must deal with these issues.

Patient-controlled analgesia (PCA) also represents a major improvement over intramuscular narcotics for treating postoperative pain.[6] The cost of PCA pumps and the unfounded fears about safety are reasons why there has not been more widespread use of this technology. By optimizing pump use and development of safe protocols and procedures, an organized acute pain service can overcome these problems and offer care in ways that benefit both patients and the institution.

ORGANIZATION

Hospital Locations Where Care Is Provided

Our initial experience with EOA was with patients following extensive thoracic surgery. These were typically patients who, because of their age and a variety of underlying medical problems, were scheduled for postoperative admission to our intensive care unit (ICU). It soon became apparent that the benefits of superior analgesia to these patients extended beyond the time that ICU care was needed. It was also clear that there were many additional patients undergoing painful surgical procedures who could benefit from postoperative EOA, but who did not require ICU admission. We therefore gradually expanded availability of EOA to all postsurgical wards in the hospital, preceded in all cases by the development of nursing protocols and procedures, and by the careful and detailed nurse training that we will describe. These wards consist entirely of single or two bed rooms and are staffed entirely by registered nurses.

PCA was similarly introduced gradually to all postsurgical wards, preceded by the development of nursing protocols and appropriate nurse training.

Standard Orders

Standard orders have been developed for use throughout our institution both for EOA and PCA. Their purpose is to provide a consistent and familiar approach to care in all areas while minimizing the risk of errors of omission or duplication in the orders. In the case of EOA the orders contain (1) the narcotic to be used, its dose, and a range for the interval between injections (for example, preservative-free morphine 4 mg every 6 to 12 hours); (2) an option for treatment of inadequate analgesia; (3) instructions for patient monitoring; (4) instructions for the treatment of common side effects; and (5) a statement of the medical personnel to call in the event of a question or emergency.

For PCA, the standard orders specify (1) which narcotic to use in the pump; (2) the narcotic dose the pump will deliver when triggered;

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1. Operating Room Dose: Drug ______ mg ______ Time ______
2. Drug for Continuing Epidural Analgesia
   A. PF morphine (1 mg/ml) ______ mg every 6–12 hours.
   B. Fentanyl (10 mcg/ml normal saline) Infuse ______ mcg (______ ml) hour.
   C. Other: Drug ______ Concentration ______ Dose ______ Interval
3. For inadequate analgesia with prescribed dose above, give FENTANYL 50 mcg (1.0 ml) into epidural catheter every 3 hours as necessary.
4. Maintain IV access (drip, heparin lock) for 24 hours after last dose of epidural narcotic.
5. Naloxone 0.4 mg at bedside.
6. *No narcotics or other CNS depressants* to be given except as ordered by the Acute Pain Service.
7. Monitoring: Respiratory rate and sedation scale every hour for first 24 hours.
8. Treatment of Side Effects
   A. Call Acute Pain Service for sedation scale = 3.
   B. Call Acute Pain Service for RR < 8 per minute.
   C. Naloxone 0.4 mg *IV stat* for sedation scale = 3 *plus* RR < 8 per minute. Call Acute Pain Service.
   D. Transdermal scopolamine patch to either mastoid area for nausea/vomiting. Change every 72 hours as necessary.
   E. Naloxone 0.1 mg IV for severe itching. MR every 10 minutes × 5.
   F. For urinary retention, "in and out" bladder catheter.
9. For inadequate analgesia or other problems related to epidural, call Acute Pain Service.

Appendix A. *Acute Pain Service: Epidural narcotic standard orders.*

(3) the "lockout interval" between doses; (4) the maximum amount of narcotic that can be delivered in any 4-hour period; (5) treatment options for inadequate analgesia with initial pump settings; (6) patient monitoring; (7) treatment of side effects; and (8) the medical personnel to call, if needed. Both sets of standard orders specify that the pain service is responsible for all matters relating to postoperative analgesia. Samples of EOA and PCA standard orders can be found in Appendixes A and B.

Safety Issues

Monitoring. Although early reports mentioned the occurrence of sudden respiratory arrest in patients receiving EOA, all recent reports of which we are aware describe slowly increasing ventilatory insufficiency. Our experience now exceeds 2500 surgical patients and an additional 900 patients who received a single injection of epidural or subarachnoid morphine following cesarean section. In the few cases of respiratory depression that we have observed, gradually increasing somnolence was a prominent feature. Our current monitoring practice relies primarily on well-trained nurses who check both respiratory rate and a simple bedside sedation scale hourly for the first 24 hours in all patients receiving an epidural or intrathecal narcotic. The sedation scale we use is reproduced in Table 1.

Apnea monitors, used on our first 1000 patients, were not as useful as expected. It is not surprising that they failed to detect our most serious cases of respiratory depression because respiratory rate is a

1. Drug
   ______ Morphine (1 mg/ml)
   ______ Meperidine (10 mg/ml)
   ______ Other: Drug ______ Concentration ______
2. Incremental Dose ______ mg ie, ______ ml.
3. Lockout Interval, 8 minutes
4. Four-Hour Limit, 30 ml.
5. If pain not controlled after 1 hour, increase incremental dose to ______ ie, ______ ml.
6. If pain still not controlled after 1 additional hour, reduce lockout interval to ______ minutes.
7. No systemic narcotics or other CNS depressants to be given except as ordered by Acute Pain Service.
8. Monitoring: Respiratory rate, analgesic level, sedation scale—every 2 hours for 8 hours; then every 4 hours. Record on ICU sheet.
9. Documentation: Record drug use on ICU sheet at each monitoring interval and 8-hour drug totals on MAR.
10. Treatment of side effects
    A. Droperidol 0.25 mg for severe nausea and vomiting. MR × 1 at 10 minutes.
    B. "In and out" bladder catheter "prn" for urinary retention.
    C. Call Acute Pain Service for sedation scale = 3.
    D. Call Acute Pain Service for RR < 8.
    E. Give naloxone 0.1 mg *IV stat* for sedation scale = 3 *plus* RR < 8. MR × 3. Call Acute Pain Service.
    F. Diphenhydramine 25 mg IV for severe itching. MR × 1.
11. For inadequate analgesia or other problems related to PCA, call Acute Pain Service.

Appendix B. *Acute Pain Service: Intravenous PCA standard orders.*

poor indicator of respiratory depression in patients receiving epidural narcotics. This, coupled with problems of frequent false alarms, has resulted in a decline in the use of apnea monitors in our practice.

Stenseth et al[13] reported a series of 1085 surgical patients treated with epidural morphine and subsequently monitored by human observers. In the patients in that series who developed respiratory depression, and in those we have observed, the onset of depression was gradual, the problem was recognized by ward nurses, and effective treatment was provided without injury or death.

Some patients may be at increased risk of respiratory depression. They include elderly patients, patients with significant systemic disease, and those who have undergone extensive or lengthy surgery. In

Table 1. *Example of Bedside Sedation Scale*

SEDATION	DESCRIPTION
0 (None)	Patient alert
1 (Mild)	Occasionally drowsy; easily aroused
2 (Moderate)	Frequently drowsy; easily aroused
3 (Severe)	Somnolent; difficult to arouse
S (None)	Normal sleep; easily aroused

addition, patients who have received large epidural narcotic doses or who have been treated with parenteral narcotics or other long-acting CNS depressants may be at extra risk. Special care should be used if these factors are present. Some of them place patients at risk for a variety of postoperative complications and increase the probability of their admission to intensive care facilities immediately after surgery whether or not epidural narcotics are used.

Checks of respiratory rate and level of sedation every 2 hours for the first 8 hours, then every 4 hours, constitute our monitoring practice for patients using PCA (see Appendix B).

Order-Writing. To avoid potentially dangerous duplication, it is necessary to establish that all pain-related orders, including orders for sedatives, hypnotics, and other CNS depressants, come from one source. In our case it is the Acute Pain Service. Responsibility for analgesic therapy reverts to the surgeon when patients can obtain satisfactory pain relief with oral analgesics.

Catheter Identification. To minimize the risk of accidental epidural injection of drugs intended for intravenous administration,[7] a bright yellow intermittent injection cap (Product IN1000, Burron Medical, Inc., Bethlehem, PA) that is distinctly different from intravenous injection ports is placed on the epidural catheter connector, and a brightly colored label that reads Epidural Catheter is placed on the catheter near the injection cap. The initial epidural narcotic dose is given by the operating room anesthesiologist about 1 hour prior to the completion of surgery. Subsequent doses are injected by ward nurses after receiving special training in the technique.

Medical Support. Clinical rounds on all patients on the Acute Pain Service are made each morning and thereafter throughout the day as necessary. For each patient, quality of analgesia and side effects are assessed, effective narcotic dose is noted, the epidural catheter site is inspected, and chart documentation of care is completed. Acute Pain Service physicians are available at all times to answer questions from ward nurses, consult with surgeons, or see patients who are experiencing problems with any aspect of their pain relief.

Nursing Policies and Procedures

Developing hospital-wide nursing policies and procedures helps standardize clinical practice using techniques such as EOA and PCA. Standardization promotes safety and creates a framework from which individualized patient care follows. Policies, the foundation or "ground rules" for practice, accompanied by stepwise procedures that outline the "how to" are located in manuals on each nursing unit. The policies and procedures (alternately called nursing protocols) also serve as ongoing educational and informational references.

A list of topics related to EOA that are covered by nursing policies and procedures are found in Table 2. Additional issues such as monitoring, order-writing, medical support, and accountability of EOA injections have been described previously.

Epidural catheter injection technique must be clearly defined,

Table 2. *Topics Addressed by Nursing Policies and Procedures for Epidural Opiate Analgesia*

Patient monitoring
Available medical support
Use of supplemental narcotics/sedatives
Accountability for injection of EOA
Maintenance of continuous epidural narcotic infusions
Epidural catheter injection technique
Dilution versus nondilution of narcotics
Filters: in-line or needle type
Identification of epidural catheters
Care of epidural catheter and insertion site
Removal of epidural catheter

using clearly worded steps. Instructions should cover all aspects of preparing and administering the injection, including aseptic precautions and the type and size of needles and syringes to be used. A filter needle is recommended for withdrawing drugs from glass ampules to avoid the risk of contamination with glass microparticles.[11] While in-line filters connected to an epidural catheter will also prevent injection of glass microparticles, they may prevent recognition of blood or CSF with aspiration prior to each narcotic injection.

Injection procedures should define the steps to dilute narcotics into larger volumes if required by the practice of the institution. The utility of diluting narcotics remains controversial. The risk-benefit ratio of this decision should be considered carefully because each step involved in diluting a drug adds the possibility of an error.

One of the most important factors to ensure safe epidural catheter injections is a careful aspiration test. This should be emphasized in the protocol. Instructions should be provided for what to do and who to call if blood or clear fluid can be aspirated. In our experience to date, nurses have been administering over 12,000 doses of epidural narcotics. Three catheters that migrated to intravascular or subarachnoid positions were detected using an aspiration test.

Catheter and insertion site care require definition in nursing protocols. An appropriate aseptic technique should be used for narcotic injection. The site of catheter insertion must be inspected regularly for signs of correct placement, inflammation, or infection. Transparent dressing facilitate this care. These are changed only when they become loose. The Acute Pain Service removes epidural catheters in our hospital. Nursing policies and procedures that define technique and potential risks should be developed if staff nurses remove catheters.

Nursing policies must define who should be called for patient problems related to inadequate analgesia, need for sedation, unresolved side effects, or catheter problems. It is helpful to create a list of experienced resource nurses in the hospital who can be contacted for assistance or advice when problems arise on a surgical ward.

Nursing policies and procedures for PCA should address basic principles such as pump operation, patient monitoring, and treatment of side effects. As with EOA, appropriate medical support should be defined.

Instructions for initial PCA pump setup can be outlined in steps. These include loading syringes into pumps and initial pump settings for dose size, lockout interval, and any other dose restrictions. Pump instructions and troubleshooting guides provided by the manufacturer should be familiar and readily available. Guidelines are needed for patient selection, monitoring, treatment of side effects, and documentation of patient status and narcotic use. Policies should address security issues such as handling of pump keys or use of access codes.

MANPOWER AND TRAINING

Pain Management Physicians

A postoperative pain management service makes considerable demands, both administrative and clinical, on those responsible for its operation. Initial administrative duties include liaison with nursing services in the development of policies and protocols, standard orders, monitoring practice, and medical responsibility. Hospital administration must be consulted to initiate the purchase or leasing of equipment (for example, PCA pumps). Teaching programs for ward nurses must be developed, updated as needed, and frequently offered. Mechanisms for disseminating information to surgeons and surgical patients are necessary. An educational program is also needed for the operating room anesthesiologists. In an academic department, the education of medical students, anesthesiology residents, and fellows must be planned. Appropriate research should be encouraged and supported early in the evolution of a new service.

Once a program has been established, physicians must be available to provide daily patient care and a call-response capability. In a busy hospital this can easily become a full-time activity.

Operating Room Anesthesiologists

Close cooperation and communication are essential between the operating room anesthesiologist and the postoperative pain management team that assumes responsibility for analgesia when surgery is completed. Recommendations for postoperative analgesia including benefits, risks, and alternatives are best made to patients at the time of the preanesthetic visit. These are then discussed with the surgeon before implementation. In the case of EOA, it is essential that correct placement of the epidural catheter is confirmed by testing it with an appropriate local anesthetic. Parenteral narcotics and other long-acting CNS depressants should be avoided or used in small doses in the perioperative period because they may increase the risk of respiratory depression with subsequent epidural narcotic administration. The operating room anesthesiologists must understand the reasons for and importance of these measures, which for some will require a change in practice.

When PCA is planned, notification of the nursing staff results in instruction of the patients in the correct use of the PCA pump prior to surgery and immediate availability of a pump when the patients return to the ward after surgery. Although PCA can be started in the recovery room, small intravenous narcotic boluses titrated to produce analgesia until patients return to the ward are convenient and effective. This practice eliminates the need for pumps to be moved with patients and problems with patients in the recovery room who are too sedated to self-administer narcotics.

Nurses

Epidural Opiate Analgesia. Ongoing education is integral to patient safety. Nursing education must precede implementation of EOA or PCA in the clinical setting. Our education program for nursing management of patients receiving EOA consists of a slide-tape program accompanied by written material and practical experience under supervision. The slide-tape program covers pertinent anatomy, physiology, and pharmacology related to EOA. Nursing activities that are covered include catheter injection technique, management of side effects, and patient education. Nurses practice injections using an epidural catheter simulation. Correct technique is verified with the simulation and in the clinical setting by a clinical nurse specialist or nurse preceptor. When first introducing EOA into a hospital, a "train-the-trainer" approach can enhance efficiency and logistics of nurse education. A formalized certification process helps ensure proper standards of care.

Patient-Controlled Analgesia. The educational thrust for nurses when introducing PCA is the setup and operation of PCA pumps. Most companies marketing PCA devices provide educational resources and in-service training for nursing staff. We use a videotape to assist in educating new nursing staff. It covers the rationale for PCA use and pump setup and operation. Nursing protocols for PCA contain the policies and procedures unique to our institution.

Ongoing in-service education on a unit-based level, is effective in communicating changes in procedures and practice. Informal education for nurses also occurs during daily Acute Pain Service rounds.

Surgeons

For reasons of patient safety, the standard orders for EOA and PCA specify that all orders for pain control and sedatives are to be given by the pain service. Responsibility for analgesic therapy reverts to the surgeon when patients can obtain satisfactory pain relief with an oral analgesic. To facilitate a smooth transition, the surgeon is asked to write oral analgesic orders immediately after surgery to become effective when EOA or PCA are discontinued.

Pharmacists

To facilitate prompt, safe care, the hospital pharmacy must become familiar with special preparations of narcotics for epidural injection or infusion, and the loading and operating procedures for a number of pumps sometimes used for administering them. They can assure drug compatibility when local anesthetics and narcotics are mixed and can alert physicians if they identify the possibility of adverse drug interactions. They must develop reliable stocking and dispensing procedures for narcotics administered by PCA pumps. Controlled substance regulations must be followed while using these new methods of narcotic administration.

Clinical pharmacists present on ward rounds can be an effective consulting resource in patients exposed to complex polypharmacology or experiencing unusual drug-related side effects or tolerance.

Psychologists

It is not surprising that the perioperative period can be a time of serious psychologic distress. Concerns about underlying disease, pain, disability, loss of income, hospital costs, or death are obvious sources. Surprisingly little has been done to characterize, diagnose, or treat these problems in surgical patients. This appears to be an important aspect of the comprehensive care of surgical patients and should be considered in planning a postoperative pain management service.

ECONOMIC CONSIDERATIONS

Physicians

When professional time is committed to a new clinical activity, financial compensation for that time must be considered. There is a strong medical tradition to support the concept that professional fees for services should be provided to specialists whose knowledge and skills are necessary to optimally treat complex medical problems. Just as critical care anesthesiologists collect professional fees for managing patients on mechanical ventilators after surgery, it is also reasonable to collect professional fees for postoperative pain management. It is the responsibility of those who treat postoperative pain to develop fair and reasonable charges for the care they provide.

Nurses

Does a program offering EOA, PCA, and other forms of contemporary acute pain relief require extra nursing manpower? This question has not yet been answered scientifically, but it is the strong impression of nurses in our institution that it does not. Certainly, it has not been necessary to increase the nurse-patient ratio, nor has the existing nursing resource been additionally taxed. In response to a questionnaire on the subject, a large majority of nurses believe less nursing time is required when PCA is used compared with patients receiving intramuscular injections of narcotics after surgery. The same opinion applies to EOA. While more frequent patient assessments were initially viewed as a burden on time, nurses now indicate the time needed for these assessments is simply a reallocation of time already spent in patient care. For example, with improved comfort, less time is spent dealing with patients' pain-related complaints. In addition, many patients with well-controlled pain are able to undertake activities, such as coughing, deep breathing, incentive spirometry, and ambulation, independently or with minimal help, thus freeing the nurse to attend to other duties.

Patients and Insurance Carriers

Patients are becoming increasingly aware of advances in postoperative pain control. With this awareness comes the demand for contemporary care when surgery becomes necessary. It is predicted that consumer pressure to provide these services will continue to grow.

A number of studies demonstrate that when effective treatment of pain after surgery is provided, in addition to superior analgesia, there is a reduction in incidence of certain complications, number of hospital days, and hospital costs.[9, 15] Health insurance carriers are expected to support reasonable reimbursement for care that reduces the size of claims.

Hospitals

With the advent of DRG reimbursement, hospital administrators are expected to be intensely interested in programs that can reduce the costs of caring for patients. In addition to direct financial benefits, availability of programs that provide superior analgesia may offer a competitive edge to institutions seeking to attract surgical patients. It is expected that these factors will lead to considerable future institutional support for acute pain management programs.

SUMMARY

New services developed to improve the treatment of acute pain in hospitalized patients have been described and are of current interest to anesthesiologists. To establish such a service, a considerable administrative commitment is necessary. It includes a close liaison with nursing staff to develop appropriate educational and procedural standards, and important interactions with surgeons, hospital pharmacists, and those providing the surgical anesthetics. A well-planned and organized service should be seen as beneficial to patients, physicians, nurses, and hospitals.

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Outcome of Pain Management

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The precise day and time when modern anesthetics were introduced into medical practice remains a matter of some dispute. Without dispute, however, is the raison d'etre of this remarkable achievement, namely, relief of operative pain. The provision of insensibility during the conduct of an operative procedure was of such obvious benefit that the dangers and shortcomings of the early anesthetics were only slowly recognized. Diethyl ether is a perfect example. Given the nature of medical practice in the nineteenth century it was truly serendipitous that an agent was introduced that created sympathetic support of the circulation, stimulated respirations, relaxed skeletal muscles, and provided a significant measure of analgesia well into the postoperative period. These properties no doubt account for the continued popularity of ether well into the twentieth century despite some serious drawbacks to its use. Although the humane benefit of anesthesia was obvious for all to see, equally obvious was the fact that insensibility during the operation did not necessarily change the overall course of events for many patients. Mortality rates for a "capital" operation routinely ran in the range of 30 to 50 per cent, in large part, owing to infectious complications. However, the introduction of antiseptic was the next dramatic accomplishment in the care of surgical patients. With the dual advantages of operative insensibility and sterile technique, surgeons (and patients) were far more willing to consider surgery as an option for the treatment of disease. Once these milestones were reached and passed, the spectacle of a major operative procedure became commonplace and the specter of postoperative complications became all too real. Perhaps the first real intensive investigation into the physiology of postoperative complications was conducted in Cleveland by Dr. George Crile. After he witnessed the death of a close friend due to postsurgical complications Crile set out to define the nature of the human response to trauma (both elective and accidental) and a mechanism by which to control the unfavorable effects of this response. His work was published at the turn of the century in a monograph entitled *Anoci-Association.*[10] In his book, Crile, a surgeon, describes a technique of perioperative care that he believed would result in reduced overall operative morbidity and mortality. The technique involved anesthesia (a combination of nitrous oxide and regional field blocks with a local anesthetic), surgery (gentle manipulation of tissues and sharp dissection), and *postoperative analgesia* (utilizing a form of neurolysis for prolonged afferent blockade). Crile was one of the first to suggest that control of pain after an operation could have an overall favorable effect on the results of a surgical procedure.

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The idea that control of postoperative pain is important in preventing or ameliorating postoperative morbidity has, until recently, been slow to gain acceptance. This is most likely because of the distraction caused by other important developments in the twin disciplines of anesthesia and surgery as well as the fact that techniques for control of postsurgical pain have, until recently, been fairly rudimentary. Now, the juxtaposition of several events has led us to appreciate the potential role that perioperative anesthetic and analgesic management may play in determining postsurgical outcome. These events include (1) the introduction of new techniques for control of pain, most notably spinal narcotic administration and continuous catheter delivery systems; (2) the involvement of anesthesiologists in the postoperative care of surgical patients in the intensive care unit where they can see, first hand, the appearance of postoperative complications and ponder ways in which to prevent their occurrence; (3) an increasing involvement of anesthesiologists in the control of pain of any etiology and a consequent increased understanding of not only pain mechanisms but the means by which to control pain; (4) the willingness of surgeons to recommend surgery for patients whose degree of preoperative illness almost guarantees the occurrence of postoperative complications; (5) third-party pressure, and occasionally intervention, designed to create incentives for a reduction in hospital-based costs; and (6) a continual maturation of the specialty of anesthesiology. With this background of historical precedent and contemporary events, it is no surprise that anesthesiologists have chosen to expand their practice beyond the recovery room and become involved in all of the postsurgical recovery period.

OPERATIVE PAIN

The physiology of pain is well described elsewhere and will not be presented in any detail here. However, it is worthwhile to point out that when managing the effects of operative pain, one has essentially three different sites for potential intervention: (1) Afferent impulses, conducted along major nerve pathways from the site of trauma are amenable to interruption by any of a variety of agents and techniques well known to the practicing anesthesiologist. (2) Central integration in the brain occurs as part of the organism's response to pain and may be readily modulated, most commonly by the systemic administration of agents designed to reduce either the perception of pain, the physiologic effects of pain, or both. (3) Finally, the efferent response of the organism, largely modulated by the neuroendocrine system, may be manipulated in a variety of ways such as antiadrenergic agents, fluid restriction, vasodilators, and so forth, all of which are designed to counter adverse effects of the efferent response component of this system. Anyone who cares for postoperative patients is familiar with a variety of options for management of all three parts of this system.

Consequences of Operative Pain

In order to favorably affect the outcome of an operation, an understanding of the physiology of the human response to surgical trauma is necessary. Many able and dedicated investigators have worked at defining these events over the course of decades. Individuals such as Bernard, Crile, Cannon, Cuthbertson, and Selye are all examples of dedication to this type of research.

The *stress response* to surgical trauma is a fairly well-characterized pattern of neuroendocrine activation that occurs to a variable degree and for a variable duration depending on the nature of the surgical trauma and attendant pain.[7] The teleological rationale for such a response is, of course, open to speculation but presumably it is designed to maintain or restore homeostasis in the shortest time possible. This may have served our progenitors well but there is also no doubt that *the stress response will in itself create disease.* This was a central thesis in Hans Selye's work and one with which most other investigators agree. Is pain per se the primary stimulus of the stress response or are there other factors that are more important? Clearly, the blood levels of stress-responding hormones rise immediately after surgical incision (but not after anesthesia induction) before other factors such as hypovolemia, hypothermia, and so forth can be implicated.[5, 17] Later, in the postoperative period, it becomes far more difficult to separate the various physiologic events that may be occurring to cause activation of these homeostatic responses. Nonetheless, there are good clinical data to suggest that pain is at least a major component of this response. The important consequences of the stress response are the metabolic effects engendered and, ultimately, the effects on global organ function or dysfunction.

The metabolic consequences include such effects as protein catabolism, sodium retention, and immunodepression. The individual organ consequences of operative pain are probably also appreciated by most practitioners, albeit at a less well characterized level of understanding. Pulmonary function, for example, is markedly compromised by some forms of surgery and an important determinant of this effect appears to be the degree of postsurgical pain.[4] Cardiovascular system function is generally thought of in terms of such measurements as cardiac output, myocardial oxygen supply, heart rate, etc. Any, or all, of these may be affected by both pain and the means chosen to ameliorate pain. Among the primary determinants of renal function and urine volume are mean arterial pressure and sympathetic tone, both of which may be affected by pain. It thus becomes obvious that a study of the effects of pain, and pain control, on the function of individual organs is, in essence, a study of the basic physiologic function of the various organs. Manipulate the pain, favorably or unfavorably, and you manipulate organ function, favorably or unfavorably.

The final question is one of timing. The kinetics of pain and especially its effects are still poorly understood. Certainly we all appreciate that a measurable response to a painful stimulus will occur almost instantaneously. This is part of the teleologic value of pain. However, we still lack a basic understanding of the long-term effects of acute pain and what is needed to beneficially influence those effects. One thing that is becoming clear is that prophylaxis is better than therapy.[2] In other words, an ounce of prevention is worth a pound of cure. This view is supported by studies that demonstrate that preventing painful impulses from being processed in the central nervous system (CNS) provides better overall management of acute pain than trying to attenuate the pain after it has been perceived by the CNS.[58] How long should we aggressively treat acute pain? Aside from obvious humanitarian considerations, I think the answer depends primarily on the expected benefits of pain management. For the relatively healthy or young patient the answer can be dictated primarily by considerations of comfort and the administrative effort required. For the patient with limited organ system reserve who may poorly tolerate the effects of acute pain, then pain management needs to be positively addressed well into the postoperative period. This is no different than, for example, the postoperative hemodynamic management of a patient with severe cardiac disease. Namely, the majority of the operative morbidity is likely to arise *after* the operation, and therefore we need to direct out efforts not only to the operative, but to the convalescent period as well.

Operative Pain and Academic Pursuit

Several aspects of the study of postoperative pain management deserve mention. The first relates to the documentation of pain control. There are several techniques for accomplishing this, and they are certainly not all alike. If the goal of the reader is to interpret the literature on the beneficial effects of pain control per se, then it is usually a good idea to carefully read the way in which documentation of pain control was achieved. For example, probably the most common way to document and quantify pain intensity is with a visual analog scale. But the collection of this information is not accomplished in a standardized fashion. How were these data collected? By an independent observer? Was it the same individual each time? Were the data collected at the time the pain was perceived or was it gathered after the fact? Some studies use retrospectively reported pain scores that represent perceived and remembered pain that occurred over a period of time. The purpose here is not to review the techniques of pain quantification but simply to point out that they do vary considerably and that their implications may also vary.

Clinical studies in anesthesiology have improved tremendously in recent years. At this point in time there is generally little value in interpreting a study that does not report out with a proper clinical and statistical design. This means that studies should be prospective and randomized and, when possible, blinded—either single or double blinded. This may be very difficult to achieve, and occasionally insurmountable difficulties arise. For example, it is very difficult to be blinded to the infusion of a local anesthetic solution into the epidural space. It may also be difficult to conduct studies in which one is prospectively attempting to manipulate the control of human suffering. Nonetheless, it is possible and many excellent studies have been concluded. With this in mind it is important to remember to carefully examine the design of the different treatment groups that are under consideration. The authors of a clinical study may have found it necessary to modify the original intention of their investigation in order to satisfy the requisites of good clinical care. If this is the case, then how do those modifications affect your interpretation of their results?

Finally, one must consider the issue of differences in patient populations, operator expertise, and practice patterns that exist from one center to another. All of these important aspects of patient care may, and probably do, vary considerably in different institutions. Therefore, results obtained by one investigator may not be reproducible, or applicable, in the practice of another. If, for example, a pain management technique is reported to result in earlier ambulation after major intra-abdominal surgery at a tertiary referral center that cares primarily for extremely ill, elderly patients, those results might not be seen in a different center whose patient population tends to be much younger or healthier. These are distractors from the issue at hand and need somehow to be factored into our analysis of reported clinical studies.

CONTROL OF OPERATIVE PAIN

Traditional Techniques

Techniques for control of operative pain remained unchanged for decades. Because our knowledge of the mechanisms of pain and our ability to affect it was relatively static, there was little incentive to evaluate the effects of pain management on postsurgical outcome. During the past several years, new techniques of analgesic administration as well as our understanding of pain mechanisms have both evolved at a rapid rate. These two developments occurred simultaneously and in a synergistic fashion. We are now in a position to evaluate the potential benefits of this new knowledge and these new capabilities. It is conceivable, if not desirable, that in a few years we will no longer be using traditional techniques of postoperative pain control for the "control" group in studies on postoperative pain management.

The standard of care will have evolved to the point where we will be comparing different types of analgesia, all of which are superior to current "traditional" techniques.

Current Techniques

The currently available techniques for operative pain control that we will consider center around (1) the use intermittent administration of parenteral narcotics by a patient care provider (traditional), (2) patient-controlled administration of parenteral narcotics, and (3) spinal administration of analgesic agents (local anesthetics and narcotics). The latter two options may be administered in either a continuous or intermittent fashion although most of the currently available clinical information is based on intermittent administration. This may be of more than passing interest for at least two reasons. One is the fact that, as mentioned previously, pain is easier to prevent than it is to treat and the intermittent administration of analgesic agents means, almost by definition, that pain will have occurred or recurred before it is treated. Second, the same phenomenon may also be operant from a neuroendocrine standpoint. That is, neuroendocrine abnormalities that are engendered by pain are more difficult to bring under control than they are to prevent.[2] The majority of current techniques for postoperative pain control use either narcotics or local anesthetics (or both) as the primary medications. We shall therefore consider these two classes of agents as being those of greatest interest. Other techniques, such as systemic administration of nonsteroidal anti-inflammatory agents or spinal administration of adrenergic agents are either too new or too little clinical information is available to accurately consider their effects on outcome.

ADVANTAGES OF PAIN CONTROL

Pulmonary Function

The effect of anesthesia and surgery on postoperative pulmonary function has been studied extensively over many decades. During this time some fairly important information has come to light. Early investigators found that postoperative pulmonary function was severely depressed, especially in patients who undergo abdominal and thoracic surgery. It appears that the closer the operation is to the diaphragm, the worse the postoperative deterioration in overall pulmonary function. The degree of impairment of pulmonary function is almost surprising. Decreases in flows and volumes in the range of 20 to 60 per cent are common—a fact with which most practicing anesthesiologists are familiar. The cause of this observed clinical effect is still not known with certainty. It is probably multifactorial but certainly it appears that pain, and quite possibly the drugs used to treat pain, are involved.[4, 34]

Until recently there were few studies that specifically addressed the effect of anesthetic management on postoperative pulmonary function. Those that did usually consisted of broad retrospective reviews that compared regional anesthesia with general anesthesia in terms of the incidence of postoperative pulmonary complications.[1] No firm conclusions could be drawn from most of these studies, which is not surprising given that they were not prospectively designed and the end points were generally not well defined. It is also not surprising that there should be little detectable effect of one decision regarding intraoperative management (that is, choice of anesthetic technique). One should not expect that a single decision, at one point in time, regarding the choice of one agent will have a significant effect on overall operative outcome. To have a significant influence on operative outcome a series of important management decisions need to be made and implemented properly. One of the first attempts to study the effect of an overall anesthetic management program on postoperative pulmonary function was conducted by Simpson et al in 1961.[49] The authors utilized continuous epidural analgesia with local anesthetics for control of postlaparotomy pain. The results indicated that, when compared with retrospective controls, their patients had much earlier return of pulmonary function with vital capacity measurements returning to within 85 per cent of normal at 24 hours. There was one pulmonary complication reported in the 60 cases. The difficulty of administering continuous or intermittent local anesthetics made this technique too cumbersome for widespread use. The authors did note, as most of us have subsequently found, that placement of the catheter in the thoracic epidural space allowed for utilization of lower total doses of drug with the avoidance of some of the bothersome hypotension and with the advantage of improved pain control. One of the first truly comparative studies to look at the question of anesthetic management on pulmonary function after surgery was conducted by Spence and Smith in 1971.[50] They compared the use of intramuscular morphine for postoperative pain relief with the use of epidural bupivicaine through a catheter placed at the T7 to T8 interspace. The patients were all relatively young males undergoing upper abdominal surgery using a standard operative anesthetic. The results indicated a significant improvement in postoperative arterial oxygenation and in the postoperative forced expired volume in 1 second (FEV1) to forced vital capacity (FVC) ratio in the epidural group. The incidence of pneumonia was seven of ten patients in the morphine group and 2 of 11 patients in the epidural group. Similar results with regard to pulmonary complications[42] were reported by other investigators during the same period. These early studies on the effect of pain control on operative recovery were encouraging and suggested a consistent beneficial effect with improved pain control. Unfortunately, the technique of epidural administration of local anesthetics was still too cumbersome to allow widespread acceptance.

The explosion of interest and knowledge regarding nociceptive mechanisms and pathways, endogenous opiate physiology, synthetic opiate action, local anesthetic mechanism of action, and the introduction of improved delivery systems for systemic and epidural medications have all resulted in a significant renewal of interest in postoperative pain control. Several contemporary studies have reinforced the information presented in the studies described. For example, when compared with traditional methods of intermittent parenteral administration of narcotics, the use of local anesthetics for postoperative pain control has been shown, in prospectively designed studies, to improve oxygenation after surgery for cholecystectomy[36] and total hip replacement.[37] In addition, other investigators have demonstrated that utilization of epidural analgesia results in less deterioration in FVC, FEV1, and peak expiratory flow rate (PEFR).[22, 43, 48, 53, 59] These studies have been conducted in patients undergoing both thoracic and upper abdominal surgery, the patients about whom one is most concerned. Although one might guess that an improvement in postoperative pulmonary function would result in a significant decrease in pulmonary complications such as pneumonia and atelectasis (however defined) this has not always been seen. However, virtually all studies that have addressed this question have shown at least a *reduction* in the incidence of pulmonary complications with the use of epidural analgesia, although it might not always be statistically significant. Several recent studies, prospective and randomized, have demonstrated that the postoperative analgesic regimen chosen for pain control does have a significant influence on the incidence of postoperative pulmonary complications. This has been demonstrated for patients undergoing upper abdominal surgery,[12, 22] thoracic surgery,[21] or both.[60] Although these studies have by and large used epidural narcotics for pain control, one might ask whether the combination of narcotics and local anesthetics will result in improved pain control over that achieved with narcotics alone. Whether this combination will also result in a further reduction in pulmonary complications is, as yet, unknown. Other techniques of pain control, such as infiltration of the wound with bupivicaine[41] and intercostal blocks[15] have also been shown to result in reduced postoperative pulmonary dysfunction although fewer studies have been reported using these techniques. How a single injection of local anesthetic might act to decrease morbidity during the entire recovery period is a puzzling question. The answer may lie in preventing the initiation of painful reflexes, as mentioned previously.

The mechanism of action by which any of these analgesic regimens improves postoperative pulmonary function and decreases morbidity is not clear. Pain is usually considered the primary etiology of pulmonary dysfunction after surgery. Certainly relief of pain, by whatever mechanism, will result in improved pulmonary function.[4] Although the greatest improvement is generally seen with spinally administered agents, even then pulmonary function does not generally return to normal. Part of this improvement, at least with epidural analgesia, appears to be due to an improvement in postoperative diaphragmatic function.[34] Another reason for the difference may be due to the respiratory depressant action of systemic narcotics. Catley et al[6] compared systemic morphine on patient demand with epidural bupivicaine for postoperative pain relief in patients undergoing either hip surgery or cholecystectomy.[6] They found a very high incidence of arterial hypoxemic episodes in the group receiving systemic narcotics early in the postoperative period. This is consistent with previous studies showing a lower arterial oxygen tension, decreased minute ventilation, and increased respiratory rate in patients receiving parenteral narcotics compared with epidural analgesics. It may well be that the respiratory depressant effects of systemic narcotics contribute to postoperative pulmonary dysfunction and complications and that utilization of spinally administered agents simply bypasses this undesirable effect.

Overall, the results appear consistent. Aggressive postoperative pain management, using techniques that avoid or decrease the administration of parenteral narcotics, results in a measurable improvement in postoperative pulmonary function and a decrease in pulmonary complications. These results are especially noticeable in patients with a high incidence of postoperative pulmonary morbidity.

Thromboembolic Complications

Some types of surgery have a historical precedent of concern regarding postoperative complications. This is especially true for hip surgery where one of the most dreaded and unfortunately common complications is postoperative deep vein thrombosis with or without pulmonary embolism. This fact has led orthopedic surgeons to utilize a continuously unfolding array of techniques for the reduction of thromboembolic complications. Of the three arms of Virchow's classic triad, namely, vascular damage, stasis, and hypercoagulability, only stasis and hypercoagulability are generally considered amenable to intervention. The third, vascular damage, may well be simply an unavoidable component of surgical intervention although it is interesting to note that gentle manipulation of tissues was part of Crile's original technique for the reduction of postoperative morbidity.

Reduction in thromboembolic complications has recently been linked to the type of anesthesia and postoperative analgesia that is used in patients at high risk for these complications. The best study to date on this subject was published by Modig et al[39] who demonstrated a significant reduction in the incidence of deep venous thrombosis and pulmonary embolism after total hip replacement when epidural anesthesia and analgesia was compared with general anesthesia and parenteral narcotic analgesia. Patients who received epidural analgesia were given bupivicaine for postoperative analgesia. With regard to the mechanism of this reduction, one must certainly consider that enhancement of lower extremity flow by an epidural-induced sympathectomy was involved. This may have been both relative in that positive pressure ventilation, with its known effect of decreasing lower extremity flow,[27] was avoided, and absolute, given the ability of epidural local anesthetics to induce an increase in lower extremity blood flow.[9, 40] The other potential mechanism for reduction in thromboembolism is a modification in the usual "hypercoagulability" seen after surgery. The activation of the coagulation system can be viewed as another component or result of the stress response. It is a component because trauma to tissues will directly activate the system. It is a result because stress-responding hormones such as the cathecholamines will also activate or magnify the response of this system. The extent to which control of pain per se, or the mechanism of pain control, can influence the postoperative coagulation profile is not really known. However, the use of local anesthetic-induced anesthesia and analgesia has been shown to reduce some measurable parameters of an activated coagulation system, specifically the postoperative platelet count and factor VIII activity.[13, 38] These studies and others like it[23, 35, 51] have not reported on quantitative measures of pain control and so cannot begin to distinguish between the effects of pain control by local anesthetics and the effects of a local anesthetic-induced sympathectomy with consequent increased vascular flow. One study that did address this issue was reported by Rawal et al in 1984.[43] The authors studied a group of obese patients undergoing gastric surgery. In a randomized, double-blind fashion the patients received either epidural or intramuscular morphine on demand for control of postoperative pain. Evidence of deep venous thrombosis was assessed by radionuclide scanning techniques and no significant differences were found between the two groups although the only three patients who had suggestive evidence of thrombosis were in the intramuscular morphine group.

Pain and the Neuroendocrine ("Stress") Response

Much has been published in the anesthesia literature recently regarding the (measurable) neuroendocrine response to trauma and our ability to manipulate that response by various anesthetic and analgesic techniques. Our understanding of this response undergoes constant revision as our ability to define the various components of the system and their mediators becomes more sophisticated. In order to fully appreciate the stress response and its implications, it should be thought of, as described previously, in terms of an afferent limb, central integration, and an efferent limb. It is the efferent limb that is generally measured in stress response studies. Such studies look at, for example, the elevations in serum cortisol or adrenaline that accompany surgery.[5, 17, 18, 25, 31] Other similar studies may look at metabolic consequences such as catabolism[55] or immune suppression.[28, 52] Most of the common mediators of neuroendocrine homeostasis have been measured in the perioperative period. Some of these studies simply record the response in a group of patients undergoing a reasonably standardized surgical procedure. (The latter is an important point in interpreting stress response studies because it is clear that the degree of response is dependent, to a large extent, on the degree of surgical trauma.) However, many studies will use two patient groups for whom some aspect of the perioperative care is manipulated in order to measure a potential effect on the stress response. For example, it has been clearly demonstrated that measurable stress response suppression can be achieved by inhalation anesthesia,[45] narcotic anesthesia,[19, 24] and by regional anesthesia[31] as long as the anesthetic is reasonably "deep" (approximately 2 MAC for inhalation anesthetics) *and for as long as the anesthetic (or analgesic) effect of the particular agent continues.*

The latter point brings us to the effect of pain control on the stress response. As mentioned, most studies measure the response or efferent limb without attempting to define whether part of the afferent limb or central integrative system may have been influenced to achieve the measured effect. This is an important question and one that is very difficult to answer. Central nervous system modulation may be as simple as a spinal reflex arc or as complex as the effect of anxiety or depression on adrenocorticotropin secretion. The afferent limb is also quite complex and although we may well appreciate some of its component parts such as pain, hypothermia, hypovolemia, and so forth, we are still only dimly aware of which one is operant for any given procedure, and when. Our ability to dissect out the effect of pain control on the neuroendocrine response to surgery is limited somewhat by our definition of pain and by the techniques used to control it. Most investigators would define pain as pain reported by the patient because we simply have no other readily available measure (such as, for example, afferent neural traffic along pain pathways) to rely on. This is something of a limitation but it does have the advantage of being goal-oriented. We are also limited by our techniques of pain control. Systemic administration of narcotic analgesics, for example, has many "side effects" that may have neuroendocrine consequences. Currently perhaps the best model of pure pain control is the use of spinally administered opiates, a technique that seems to be accompanied by the fewest effects that could be considered nonanalgesic in nature. Even here we must deal with such issues as urinary retention, pruritis, nausea, and the potential effects of cephalad migration of the agent. Finally, the use of local anesthetics raises questions regarding their effects on the vasculature (direct and indirect) and the effects of systemic absorption of the drug. For the time being we must accept these limitations of pain research.

Many years ago Bromage et al[5] demonstrated the potential effect of postoperative pain management on the hyperglycemic response to surgery. They studied patients undergoing upper abdominal or thoracic surgery and randomized them to receive either epidural and light general anesthesia with postoperative epidural analgesia or general anesthesia alone and parenteral narcotics for postoperative pain relief. The group receiving epidural analgesia had a persistent depression of the usual elevation in blood glucose that occurs in response to surgery when compared with the group that did not receive epidural analgesia. The authors also measured the usual elevation in serum cortisol and found that it was minimally affected by epidural analgesia for up to 19 hours into the postoperative period. They concluded that the effect of epidural analgesia was due to blockade of splanchnic reflexes and that the persistence of the hypercortisolemic response to surgery was due to unblocked vagal afferent activity. The results of this study typify much of the subsequent research on pain and the stress response. For example, one aspect of the stress response was suppressed although another was not. This has been true of many other similar studies. It appeared easier to suppress hyperglycemia than hypercortisolemia. Likewise, other studies have found it easier to suppress one component of the stress response than it is to suppress another. It is therefore clear that we are dealing with a complex biochemical system that does not respond in a uniform fashion to a single intervention. Secondly, we have learned that patients undergoing upper abdominal and thoracic surgery are the most difficult to control in terms of the stress response. It is far easier to control the response to lower abdominal or extremity surgery. Finally, as with many subsequent studies, the mechanism(s) involved in manipulating neuroendocrine homeostasis were not clear from the results presented. Although many possibilities could be inferred, they remained to be proved.

Subsequent to this study there have been numerous publications that have examined the effect of the technique of postoperative pain control (usually systemic narcotics compared with epidural local anesthetics or narcotics) on the postoperative stress response. Such studies have looked at not only glucose but glucose utilization, cortisol, adrenaline, noradrenaline, ADP, and many others.[17–20, 24, 25, 30, 33, 46, 54, 60] In general, one can draw several conclusions from these studies. First, the technique of postoperative pain control can have an influence on the stress response. Second, the metabolic and clinical consequences of stress response control are only beginning to be unraveled. For example, Tsuji et al,[55] in a well-conducted study, demonstrated a significant effect of anesthetic and analgesic choice on postoperative catabolism. In their study the use of epidural anesthesia and postoperative analgesia significantly reduced catabolism when measured for 3 days after surgery. (This could be part of the explanation for the effect of epidural analgesia in reducing the incidence of postoperative pneumonia. That is, less catabolism, including visceral protein catabolism, results in less immune suppression and fewer infections.) Third, the neural pathways involved are complex. For example, blockade of all the usually suspected afferent nerves, including the vagus, does not necessarily guarantee blockade of the stress response.[54] Fourth, spinally administered (epidural or intrathecal) local anesthetics appear to be more effective in controlling this response than the spinal administration of narcotics.[46] Fifth, spinal administration of narcotics, although less effective than local anesthetics, can still be demonstrated to be more effective than systemic administration of narcotics. Sixth, prophylaxis is more valuable than treatment. If you allow pain to occur, and *then* initiate pain control, you will see less of a measurable effect.[2, 30] Finally, when it has been evaluated, control of pain (reported pain) has correlated poorly with suppression of the stress response.[25] The reason(s) for this are simply unknown. Part of the explanation may be related to the use of reported pain as the measure of pain control. Certainly perception of pain at the cortical level can be significantly modified by events that occur elsewhere in the CNS, events that might also affect the stress response pathways. Still, our overwhelming clinical impression is that pain is a significant component of the stimulus to neuroendocrine activation and that control of pain results in control of the stress response.

Pain Control and Myocardial Function

Any discussion of myocardial function and techniques to favorably manipulate it will generally center around a discussion of the classic determinants of myocardial performance and, when coronary artery disease is under consideration, the determinants of myocardial oxygen supply. With this in mind, it is tempting to consider the effects of local anesthetic-induced neuraxial blockade on myocardial and cardiovascular function. Certainly one could build a good argument that lumbar or thoracic administration of local anesthetics results in a favorable reduction in myocardial preload, afterload, and even a favorable redistribution of intramyocardial blood flow.[32, 57] All of these effects, however, can be reasonably demonstrated to be due to interruption of sympathetic nerves and not simply to control of painful impulses.

Although we all may have an appreciation of the fact that pain represents a stress on the myocardium that may be detrimental in many circumstances, there is little evidence to suggest that control of operative pain results in a decrease in cardiovascular morbidity. Reiz et al utilized a combined epidural/light general anesthetic technique to care for a group of patients undergoing major abdominal surgery, many of whom had recently suffered a myocardial infarction. When compared with a control group undergoing the same procedures, the group given epidural anesthesia had fewer intraoperative episodes of myocardial ischemia.[44] Although a reduction in afferent nociceptive traffic may well have been responsible for some of this effect, the influence of local anesthetic-induced sympathectomy was probably also important in producing these results.

When we compared the use of postoperative epidural narcotic analgesia with parenteral narcotic analgesia in a group of high-risk surgical patients undergoing major abdominal or thoracic procedures we found a markedly lessened incidence of postoperative cardiovascular morbidity, especially congestive heart failure.[60] Our study was not designed to determine if pain control might have been a part of this effect. That is, we made no attempt to assess the pain perception of the patients in the study. The mechanism(s) involved in reduction of cardiovascular morbidity remain speculative. We believe that our results were due to decreased adrenergic tone (a likely consequence of pain control), and a decrease in morbidity of other organs, especially a decreased requirement for mechanical ventilation. Interestingly, our results with regard to the cardiovascular system have been approximated by other studies looking at the use of narcotic analgesia for postoperative pain control in cardiac surgical patients.[14, 56] A lot of work remains to be done to elucidate the effect of pain control on postoperative cardiac events. However, the results to date are encouraging.

Side Effects of Narcotics

The use of any agent for pain relief, by any method of delivery, is not without side effects. When local anesthetics are used, the most obvious side effect is frequently an accompanying block of sympathetic fibers. When narcotics are used, there are also some potential side effects that may affect overall recovery from an operation. Of these, perhaps the two most prominent are gastrointestinal motility and mental status changes. Recovery of gastrointestinal function, especially in patients who have undergone abdominal surgery, can be one of the most troubling aspects of convalescence. Because narcotics have the known effect of inhibiting gastrointestinal motility it is only logical that one question whether the mechanism of delivery of the narcotic may have a significant effect on the return of motility. The results of the studies that have addressed this question have unfortunately been equivocal. For example, one study that compared gastric emptying in patients receiving either intrathecal or intramuscular morphine after cholecystectomy showed that 1 hour after intramuscular morphine, emptying was significantly prolonged when compared with the intrathecal group.[16] Other studies looking at the return of bowel function after colon surgery have shown that the use of epidural bupivicaine alone but not epidural narcotics[47] is associated with more rapid return of bowel function. Again, the potential effect of a local anesthetic-induced sympathectomy may be a factor. After gastric surgery, Rawal et al demonstrated an earlier return of bowel function with the use of epidural morphine compared with parenteral morphine.[43] The important questions that remain to be elucidated are the effect of the total dose of narcotic, the type of surgery, and the presence or absence of a sympathectomy.

There are differences between analgesic regimens with regard to the total amount of narcotic that may be necessary to achieve analgesia.[43] The effect that a decrease in total narcotic dose may have on postoperative mental status is another important question regarding recovery from surgery. Several studies have looked at this question and again the results are conflicting. In 1980 Hole et al[29] showed fewer mental status changes after hip surgery when epidural anesthesia with bupivicaine was compared with general anesthesia with fentanyl. The operations lasted an average of over 3 hours. A more recent study in which one group of patients undergoing hip surgery received prilocaine intraoperatively and another group received nitrous oxide/oxygen and halothane showed no difference in postoperative mental status.[3] The operations in this study lasted an average of 30 to 35 minutes. Other studies that have compared the effect of postoperative narcotic analgesia via either the parenteral or epidural route have shown both no benefit from epidural analgesia[26] and an improved mental status.[8] Again there are many factors to consider such as length of operation, age of the patients, amount of narcotic administered, and indications for administration. The effect of pain control technique on postoperative mental status remains speculative.

Resource Utilization

We all recognize the increasing interest in medical care cost containment. Can we do anything to help decrease the cost of surgery and the use of hospital resources? As there is no doubt that hospital morbidity is expensive[11] anything that we do to decrease that morbidity or shorten the duration of hospitalization will lower overall hospital costs. Some studies have suggested that choice of anesthesia and analgesia may act to decrease the duration of hospitalization and hospital costs.[42, 43, 60] The implication of these results for the majority of practice settings is not yet clear.

SUMMARY

The practice of anesthesiology continues to mature as evidenced by the increased involvement of anesthesiologists in the total perioperative care of surgical patients. That care now extends well into the postoperative period with the utilization of new and more powerful techniques for the control of pain. The technique chosen for pain control after operation may have a significant influence on several aspects of recovery. These include postoperative pulmonary function and complications, the neuroendocrine response to surgery and its metabolic consequences, and thromboembolic complications. Other aspects of recovery for which encouraging but less conclusive data are available include postoperative cardiovascular function, gastrointestinal function, and mental status. It seems that the very definition of anesthesia practice is changing. The focus and benefit of our care were previously apparent primarily in the operating room. We now find that directing our efforts towards the period following operation may be of equal, or even greater, benefit to our patients.

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